CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074910

Trade Name : DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES USP

Generic Name: Diltiazem Hydrochloride Extended-Release Capsules USP 60mg, 90mg and 120mg

Sponsor : Mylan Pharmaceuticals, Inc.

Approval Date: May 2, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074910

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Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074910

APPROVAL LETTER

ANDA 74-910

MAY - 2 1997

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, West Virginia 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application dated June 12, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diltiazem Hydrochloride Extended-release Capsules, USP; 60 mg, 90 mg, and 120 mg.

Reference is also made to your amendments dated September 12, 1996 and January 15, 1997.

Your application contains a patent certification to patent #4721619 under Section 505(j)(2)(A)(vii)(IV) of the Act. Section 505(j)(4)(B)(iii) of the Act provides that approval shall be made effective immediately unless an action is brought for infringement of the patent which is the subject of the certification before the expiration of forty-five days from the date the notice provided under paragraph (2)(B)(i) is received." You have notified FDA that Mylan Pharmacetuicals has complied with the requirements of Section 505(j)(2)(B) of the Act. No action for patent infringement was brought against Mylan Pharmaceuticals within the statutory forty-five day period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diltiazem Hydrochloride Extended-release Capsules USP, 60 mg, 90 mg, and 120 mg to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Cardizem® SR Capsules, 60 mg, 90 mg, and 120 mg, respectively, of Hoechst Marion Roussel Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

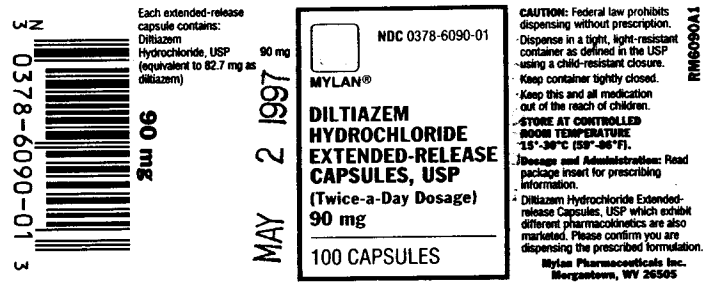
Douglas Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

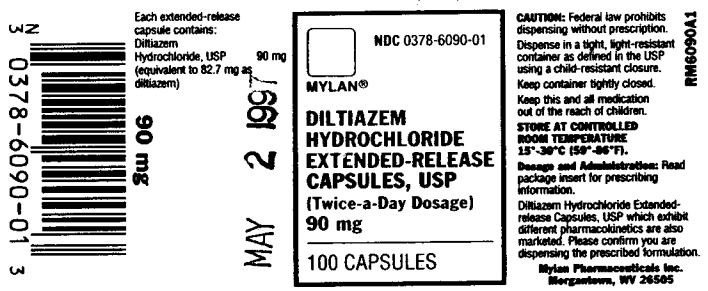
5/2/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074910

FINAL PRINTED LABELING


NDC 0378-6090-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Twice-a-Day Dosage)
90 mg
100 CAPSULES
Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 90 mg
(equivalent to 82.7 mg as diltiazem)
MAY 2 1997
CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Dosage and Administration: Read package insert for prescribing information.
Diltiazem Hydrochloride Extended-release Capsules, USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6090A1


NDC 0378-6090-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Twice-a-Day Dosage)
90 mg
100 CAPSULES
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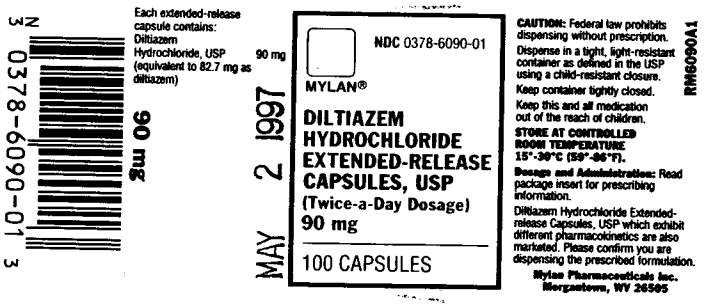
NDC 0378-6090-01
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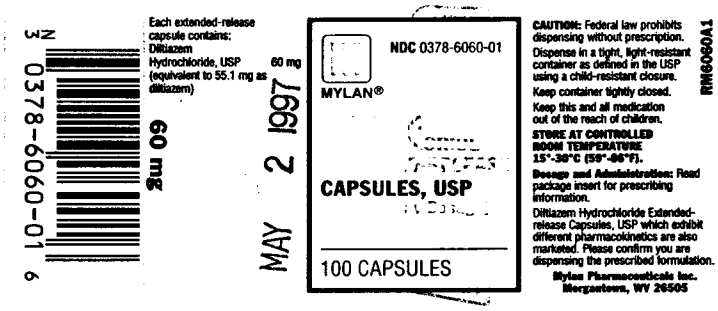
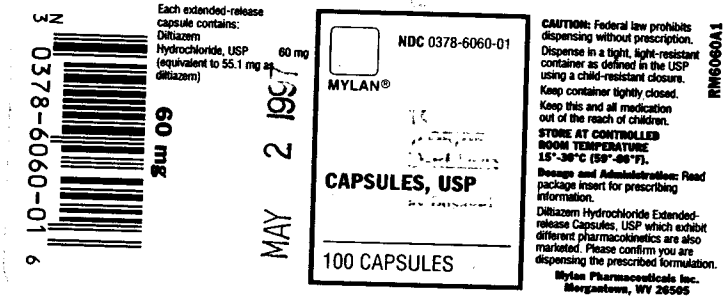
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6090A1


Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 60 mg
(equivalent to 55.1 mg as diltiazem)
NDC 0378-6060-01
MYLAN®
CAPSULES, USP
100 CAPSULES
MAY 2 1997
60 mg
0378-6060-01
CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Dosage and Administration: Read package insert for prescribing information.
Diltiazem Hydrochloride Extended-release Capsules, USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6060A1


Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 60 mg
(equivalent to 55.1 mg as diltiazem)
NDC 0378-6060-01
MYLAN®
CAPSULES, USP
100 CAPSULES
MAY 2 1997
60 mg
0378-6060-01
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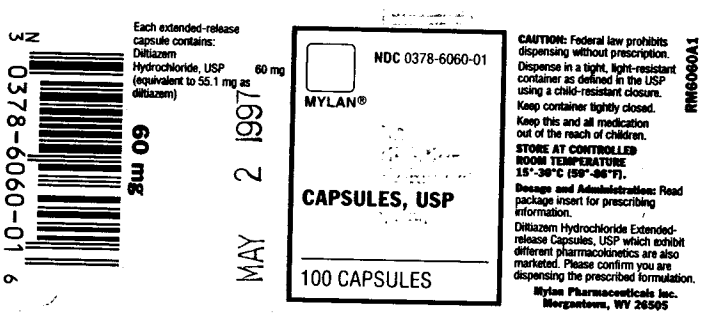
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6060A1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NDC 0378-6060-01
MYLAN®
CAPSULES, USP
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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6060A1

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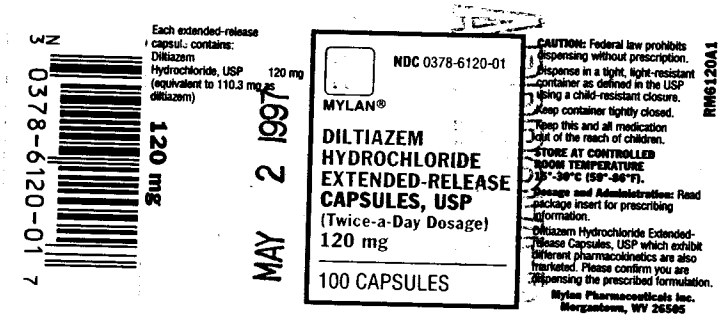
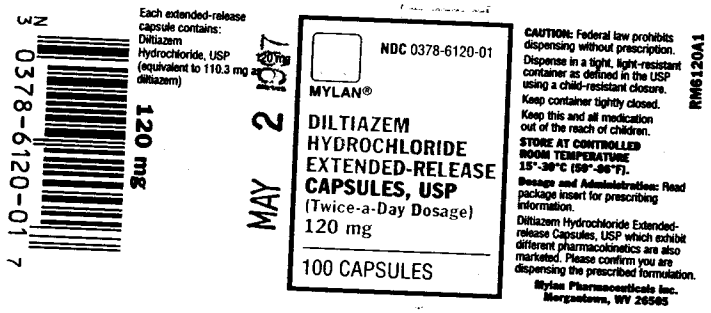

N 3 0378-6120-01 7
120 mg
Each extended-release capsul. contains:
Diltiazem Hydrochloride, USP 120 mg
(equivalent to 110.3 mg as diltiazem)
MAY 2 1997
NDC 0378-6120-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
(Twice-a-Day Dosage)
120 mg
100 CAPSULES
CAUTION: Federal law prohibits dispensing without prescription.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F).
Dosage and Administration: Read package insert for prescribing information.
Diltiazem Hydrochloride Extended-release Capsules, USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6120A1


N 3 0378-6120-01 7
120 mg
Each extended-release capsule contains:
Diltiazem Hydrochloride, USP
(equivalent to 110.3 mg as diltiazem)
MAY 2 1997
NDC 0378-6120-01
MYLAN®
DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP
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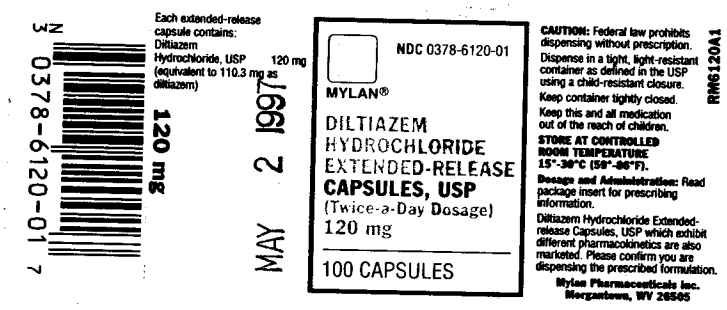
N 3 0378-6120-01 7
120 mg
Each extended-release capsule contains:
Diltiazem Hydrochloride, USP 120 mg
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MAY 2 1997
NDC 0378-6120-01
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(Twice-a-Day Dosage)
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Mylan Pharmaceuticals Inc.
Morgantown, WV 26505
RM6120A1

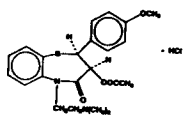
DILER:R1

DILTIAZEM HYDROCHLORIDE EXTENDED-RELEASE CAPSULES, USP

(Twice-a-Day Dosage)

60 mg, 90 mg and 120 mg

DESCRIPTION: Diltiazem Hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)-ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride, (+)-cis-. The structural formula is:



$C_{22}H_{26}N_2O_4S \cdot HCl$

Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol and chloroform. It has a molecular weight of 450.99. Each extended-release capsule, for oral administration, contains 60 mg, 90 mg, or 120 mg diltiazem hydrochloride. In addition, each capsule contains the following inactive ingredients: Diethyl phthalate, gelatin, hydroxypropyl methylcellulose, maltodextrin, methacrylic acid copolymer Type B, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, silicon dioxide, sodium lauryl sulfate, sugar spheres (25/30 mesh), synthetic black iron oxide, titanium dioxide, FD&C Red #40, FD&C Blue #2 Aluminum Lake, FD&C Red #40 Aluminum Lake, FD&C Blue #1 Aluminum Lake, D&C Yellow #10 Aluminum Lake. In addition, the 90 mg product contains D&C Yellow #10 coloring agent.

Diltiazem Hydrochloride Extended-release Capsules, USP (Twice-a-Day Dosage) 60 mg, 90 mg, and 120 mg meet *USP Drug Release Test 4*.

CLINICAL PHARMACOLOGY: The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanism of Action: Diltiazem hydrochloride produces its antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. The magnitude of blood pressure reduction is related to the degree of hypertension; thus hypertensive individuals experience an antihypertensive effect, whereas there is only a modest fall in blood pressure in normotensives.

Hemodynamic and Electrophysiologic Effects: Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal,

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Hemodynamic and Electrophysiologic Effects: Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure in normotensive individuals and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given workload. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. Increased heart failure has, however, been reported in occasional patients with preexisting impairment of ventricular function. There are as yet few data on the interaction of diltiazem and beta-blockers in patients with poor ventricular function. Resting heart rate is usually slightly reduced by diltiazem.

Diltiazem Hydrochloride Extended-release Capsules produce antihypertensive effects both in the supine and standing positions. Postural hypotension is infrequently noted upon suddenly assuming an upright position. No reflex tachycardia is associated with the chronic antihypertensive effects. Diltiazem Hydrochloride Extended-release Capsules decrease vascular resistance, increase cardiac output (by increasing stroke volume), and produce a slight decrease or no change in heart rate. During dynamic exercise, increases in diastolic pressure are inhibited while maximum achievable systolic pressure is usually reduced. Heart rate at maximum exercise does not change, or is slightly reduced. Chronic therapy with diltiazem produces no change or an increase in plasma catecholamines. No increased activity of the renin-angiotensin-aldosterone axis has been observed. Diltiazem Hydrochloride Extended-release Capsules antagonizes the renal and peripheral effects of angiotensin II. Hypertensive animal models respond to diltiazem with reductions in blood pressure and increased urinary output and natriuresis without a change in urinary sodium/potassium ratio.

Intravenous diltiazem hydrochloride in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of diltiazem hydrochloride in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of diltiazem hydrochloride in doses of up to 360 mg/day has resulted in small increases in PR interval, and on occasion produces abnormal prolongation (see WARNINGS).

Pharmacokinetics and Metabolism: Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is

Pharmacokinetics and Metabolism: Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%. Diltiazem undergoes extensive metabolism in which 2% to 4% of the unchanged drug appears in the urine. *In vitro* binding studies show diltiazem is 70% to 80% bound to plasma proteins. Competitive *in vitro* ligand binding studies have also shown diltiazem binding is not affected by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. The plasma elimination half-life following single or multiple drug administration is approximately 3.0 to 4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem appear to be in the range of 50-200 ng/mL. There is a departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. A study that compared patients with normal hepatic function to patients with cirrhosis found an increase in half-life and a 69% increase in bioavailability in the hepatically impaired patients. A single study in nine patients with severely impaired renal function showed no difference in the pharmacokinetic profile of diltiazem compared to patients with normal renal function.

Diltiazem Hydrochloride Extended-release Capsules, USP (Twice-a-Day Dosage): A single 120 mg dose of the capsule results in detectable plasma levels within two to three hours and peak plasma levels at six to 11 hours. The apparent elimination half-life after single or multiple dosing is five to seven hours. A departure from linearity similar to that observed with the diltiazem hydrochloride tablet is observed. As the dose of Diltiazem Hydrochloride Extended-release Capsules is increased from a daily dose of 120 mg (60 mg b.i.d.) to 240 mg (120 mg b.i.d.) daily, there is an increase in area-under-the-curve of 2.6 times. When the dose is increased from 240 mg to 360 mg daily, there is an increase in area-under-the-curve of 1.8 times. The average plasma levels of the capsule dosed twice daily at steady state are equivalent to the tablet dosed four times daily when the same total daily dose is administered.

INDICATIONS AND USAGE: Diltiazem Hydrochloride Extended-release Capsules, USP (Twice-a-Day Dosage) are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive medications, such as diuretics.

CONTRAINDICATIONS: Diltiazem is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, (3) patients with hypotension (less than 90 mm Hg systolic), (4) patients who have demonstrated hypersensitivity to the drug, and (5) patients with acute myocardial infarction and pulmonary congestion documented by X-ray on admission.

WARNINGS: Cardiac Conduction: Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (nine of 2,111 patients or 0.43%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem. (See ADVERSE REACTIONS.)

Congestive Heart Failure: Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). An acute study of oral diltiazem in patients with impaired ventricular function (ejection fraction 24% +/- 6%) showed improvement in indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of diltiazem in combination with beta-blockers in patients with

indices of ventricular function without significant decrease in contractile function (dp/dt). Experience with the use of diltiazem in combination with beta-blockers in patients with impaired ventricular function is limited. Caution should be exercised when using this combination.

Hypotension: Decreases in blood pressure associated with diltiazem therapy may occasionally result in symptomatic hypotension.

Acute Hepatic Injury: Mild elevations of transaminases with and without concomitant elevation in alkaline phosphatase and bilirubin have been observed in clinical studies. Such elevations were usually transient and frequently resolved even with continued diltiazem treatment. In rare instances, significant elevations in enzymes such as alkaline phosphatase, LDH, SGOT, SGPT, and other phenomena consistent with acute hepatic injury have been noted. These reactions tended to occur early after therapy initiation (1 to 8 weeks) and have been reversible upon discontinuation of drug therapy. The relationship to diltiazem is uncertain in some cases, but probable in some. (See PRECAUTIONS.)

PRECAUTIONS: General: Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any drug given over prolonged periods, laboratory parameters of renal and hepatic function should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions: Due to the potential for [illegible] caution and careful [illegible] noted in patients [illegible] diltiazem concomitantly [illegible] known to affect [illegible] contractility and conduction (see WARNINGS). Pharmacokinetic studies indicate that there may be additional effects in prolonging [illegible] when using beta-blockers concomitantly [illegible] (see WARNINGS).

As with [illegible] care should be exercised [illegible] patients with [illegible]. Diltiazem undergoes [illegible] by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course

doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Dermatological events (see ADVERSE REACTIONS section) may be transient and may disappear despite continued use of diltiazem. However, skin eruptions progressing to erythema multiforme and/or exfoliative dermatitis have also been infrequently reported. Should a dermatologic reaction persist, the drug should be discontinued.

Drug Interactions: Due to the potential for [illegible] and careful [illegible] in patients [illegible] concomitantly [illegible] known to affect [illegible] and conduction [illegible]. Pharmacokinetic studies indicate [illegible] there [illegible] in prolonging [illegible] when used [illegible] beta-blockers, including concomitantly [illegible] (see WARNINGS).

As with [illegible] care should be exercised [illegible] patients with [illegible]. Diltiazem undergoes [illegible] by cytochrome P-450 mixed function oxidase. Coadministration of diltiazem with other agents which follow the same route of biotransformation may result in the competitive inhibition of metabolism. Especially in patients with renal and/or hepatic impairment, dosages of similarly metabolized drugs, particularly those of low therapeutic ratio may require adjustment when starting or stopping concomitantly administered diltiazem to maintain optimum therapeutic blood levels.

Beta-Blockers: Controlled and uncontrolled domestic studies suggest that concomitant use of diltiazem and beta-blockers is usually well tolerated, but available data are not sufficient to predict the effects of concomitant treatment in patients with left ventricular dysfunction or cardiac conduction abnormalities.

Administration of diltiazem hydrochloride concomitantly with propranolol in five normal volunteers resulted in increased propranolol levels in all subjects and bioavailability of propranolol was increased approximately 50%. *In vitro*, propranolol appears to be displaced from its binding sites by diltiazem. If combination therapy is initiated or withdrawn in conjunction with propranolol, an adjustment in the propranolol dose may be warranted (see WARNINGS).

Cimetidine: A study in six healthy volunteers has shown a significant increase in peak diltiazem plasma levels (58%) and area-under-the-curve (53%) after a 1-week course

of cimetidine at 1,200 mg per day and a single dose of diltiazem 60 mg. Ranitidine produced smaller, nonsignificant increases. The effect may be mediated by cimetidine's known inhibition of hepatic cytochrome P-450, the enzyme system responsible for the first-pass metabolism of diltiazem. Patients currently receiving diltiazem therapy should be carefully monitored for a change in pharmacological effect when initiating and discontinuing therapy with cimetidine. An adjustment in the diltiazem dose may be warranted.

Digitalis: Administration of diltiazem with digoxin in 24 healthy male subjects increased plasma digoxin concentrations approximately 20%. Another investigator found no increase in digoxin levels in 12 patients with coronary artery disease. Since there have been conflicting results regarding the effect of digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing diltiazem therapy to avoid possible over- or under-digitalization (see WARNINGS).

Anesthetics: The depression of cardiac contractility, conductivity, and automaticity as well as the vascular dilation associated with anesthetics may be potentiated by calcium channel blockers. When used concomitantly, anesthetics and calcium blockers should be titrated carefully.

Cyclosporine: A pharmacokinetic interaction between diltiazem and cyclosporine has been observed during studies involving renal and cardiac transplant patients. In renal and cardiac transplant recipients, a reduction of cyclosporine dose ranging from 15% to 48% was necessary to maintain cyclosporine trough concentrations similar to those seen prior to the addition of diltiazem. If these agents are to be administered concurrently, cyclosporine concentrations should be monitored, especially when diltiazem therapy is initiated, adjusted or discontinued. The effect of cyclosporine on diltiazem plasma concentrations has not been evaluated.

Carbamazepine: Concomitant administration of diltiazem with carbamazepine has been reported to result in elevated serum levels of carbamazepine (40% to 72% increase), resulting in toxicity in some cases. Patients receiving these drugs concurrently should be monitored for a potential drug interaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in *in vitro* bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy: ***Teratogenic Effects - Pregnancy Category C.*** Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use diltiazem in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Diltiazem is excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. If use of diltiazem is deemed essential, an alternative method of infant feeding should be instituted.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either diltiazem hydrochloride tablets or diltiazem hydrochloride extended-release capsules, as well as

been established.

ADVERSE REACTIONS: Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded from these studies.

The adverse events described below represent events observed in clinical studies of hypertensive patients receiving either diltiazem hydrochloride tablets or diltiazem hydrochloride extended-release capsules, as well as experiences observed in studies of angina and during marketing. The most common events in hypertension studies are shown in a table with rates in placebo patients shown for comparison. Less common events are listed by body system; these include any adverse reactions seen in angina studies that were not observed in hypertension studies. In all hypertensive patients studied (over 900), the most common adverse events were edema (9%), headache (8%), dizziness (6%), asthenia (5%), sinus bradycardia (3%), flushing (3%), and first degree AV block (3%). Only edema and perhaps bradycardia and dizziness were dose related. The most common events observed in clinical studies (over 2,100 patients) of angina patients and hypertensive patients receiving diltiazem hydrochloride tablets or diltiazem hydrochloride extended-release capsules were (i.e., greater than 1%) edema (5.4%), headache (4.5%), dizziness (3.4%), asthenia (2.8%), first degree AV block (1.8%), flushing (1.7%), nausea (1.6%), bradycardia (1.5%), and rash (1.5%).

Double Blind Placebo Controlled Hypertension Trials

Adverse	Diltiazem N = 315 # pts (%)	Placebo N = 211 # pts (%)
Headache	38 (12%)	17 (8%)
AV block first degree	24 (7.6%)	4 (1.9%)
Dizziness	22 (7%)	6 (2.8%)
Edema	19 (6%)	2 (0.9%)
Bradycardia	19 (6%)	3 (1.4%)
ECG abnormality	13 (4.1%)	3 (1.4%)
Asthenia	10 (3.2%)	1 (0.5%)
Constipation	5 (1.6%)	2 (0.9%)
Dyspepsia	4 (1.3%)	1 (0.5%)
Nausea	4 (1.3%)	2 (0.9%)
Palpitations	4 (1.3%)	2 (0.9%)
Polyuria	4 (1.3%)	2 (0.9%)
Somnolence	4 (1.3%)	—
Alk phos increase	3 (1%)	1 (0.5%)
Hypotension	3 (1%)	1 (0.5%)
Insomnia	3 (1%)	1 (0.5%)
Rash	3 (1%)	1 (0.5%)
AV block second degree	2 (0.6%)	—

In addition, the following events were reported infrequently (less than 1%) with diltiazem hydrochloride extended-release capsules or diltiazem hydrochloride tablets or have been observed in angina or hypertension trials.

Cardiovascular: Angina, arrhythmia, second- or third-degree AV block (see conduction warning), bundle branch block, congestive heart failure, syncope, tachycardia, ventricular extrasystoles.

Nervous System: Abnormal dreams, amnesia, depression, gait abnormality, hallucinations, nervousness, paresthesia, personality change, tremor.

Gastrointestinal: Anorexia, diarrhea, dry mouth, dysgeusia, mild elevations of SGOT, SGPT, and LDH (see Hepatic Warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, sexual difficulties, tinnitus.

The following postmarketing events have been reported infrequently in patients receiving diltiazem: allergic reactions, alopecia, angioedema (including facial or periorbital edema), asystole, erythema multiforme (including Stevens-Johnson syndrome, toxic epidermal necrolysis), extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. There have been observed cases of a generalized rash, some characterized as leukocytoclastic vasculitis. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A definitive cause and effect relationship between

dry mouth, dysgeusia, and elevations of SGOT, SGPT, and LDH (see Hepatic Warnings), thirst, vomiting, weight increase.

Dermatological: Petechiae, photosensitivity, pruritus, urticaria.

Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, hyperuricemia, impotence, muscle cramps, nasal congestion, nocturia, osteoarticular pain, sexual difficulties, tinnitus.

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OVERDOSAGE OR EXAGGERATED RESPONSE: The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg.

The toxic dose in man is not known. Due to extensive metabolism, blood levels after a standard dose of diltiazem can vary over tenfold, limiting the usefulness of blood levels in overdose cases.

There have been 29 reports of diltiazem overdose in doses ranging from less than 1 gram to 10.8 grams. Sixteen of these reports involve multiple drug ingestions.

Twenty-two reports indicated patients had recovered from diltiazem overdose ranging from less than 1 gram to 10.8 grams. There were seven reports with a fatal outcome; although the amount of diltiazem ingested was unknown, multiple drug ingestions were confirmed in six of the seven reports.

Events observed following diltiazem overdose included bradycardia, hypotension, heart block, and cardiac failure. Most reports of overdose described some supportive medical measure and/or drug treatment. Bradycardia frequently responded favorably to atropine, as did heart block, although cardiac pacing was also frequently utilized to treat heart block. Fluids and vasopressors were used to maintain blood pressure and in cases of cardiac failure inotropic agents were administered. In addition, some patients received treatment with ventilatory support, gastric lavage, activated charcoal, and/or intravenous calcium. Evidence of the effectiveness of intravenous calcium administration to reverse the pharmacological effects of diltiazem overdose was conflicting.

In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences the following measures may be considered:

Bradycardia: Administer atropine (0.6 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or norepinephrine bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION: Dosages must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily. Maximum oral

supportive measures should be employed in addition to gastrointestinal decontamination. Diltiazem does not appear to be removed by peritoneal or hemodialysis. Limited data suggest that plasmapheresis or charcoal hemoperfusion may hasten diltiazem elimination following overdose. Based on the known pharmacological effects of diltiazem and/or reported clinical experiences the following measures may be considered:

Bradycardia: Administer atropine (0.6 to 1 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

High-Degree AV Block: Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

Cardiac Failure: Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.

Hypotension: Vasopressors (e.g. dopamine or norepinephrine bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

DOSAGE AND ADMINISTRATION: Dosages must be adjusted to each patient's needs, starting with 60 to 120 mg twice daily. Maximum antihypertensive effect is usually observed by 14 days of chronic therapy; therefore, dosage adjustments should be scheduled accordingly. Although individual patients may respond to lower doses, the usual optimum dosage range in clinical trials was 240 to 360 mg/day.

Diltiazem Hydrochloride Extended-release Capsules have an additive antihypertensive effect when used with other antihypertensive agents. Therefore, the dosage of Diltiazem Hydrochloride Extended-release Capsules or the concomitant antihypertensives may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.

HOW SUPPLIED: Diltiazem Hydrochloride Extended-release Capsules, USP (Twice-a-Day Dosage) are available in 60 mg, 90 mg, and 120 mg.

The 60 mg capsules are a #3 coral opaque 3399 cap/white opaque body imprinted with MYLAN over 6060 in black ink on the cap and body. They are available as follows:

NDC 0378-6060-01
bottles of 100 capsules

The 90 mg capsules are a #2 coral opaque 3399 cap/ivory opaque body imprinted with MYLAN over 6090 in black ink on the cap and body. They are available as follows:

NDC 0378-6090-01
bottles of 100 capsules

The 120 mg capsules are a #1 coral opaque 3399 cap/coral opaque 3399 body imprinted with MYLAN over 6120 on the cap and body. They are available as follows:

NDC 0378-6120-01
bottles of 100 capsules

Diltiazem Hydrochloride Extended-release Capsules, USP which exhibit different pharmacokinetics are also marketed. Please confirm you are dispensing the prescribed formulation.

STORE AT CONTROLLED ROOM TEMPERATURE
15°-30°C (59°-86°F).

Dispense in a tight , light-resistant container as defined in the USP using a child resistant closure.

CAUTION: Federal law prohibits dispensing without prescription.

MYLAN®

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED JANUARY 1997
DILER:R1

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074910

CHEMISTRY REVIEW(S)

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 74-910

3. NAME AND ADDRESS OF APPLICANT
Mylan Pharmaceuticals Inc.
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

4. LEGAL BASIS FOR SUBMISSION
Cardizem® SR Capsules, 60 mg, 90 mg, 120 mg
Hoechst Marion Roussel Inc.
P.O. Box 8480
Kansas City, MO 64114

The drug product is currently covered by Patent #4721619, expiring on January 26, 2005. There are no exclusivity provisions.

The firm originally filed Paragraph III Certification, 6/12/96. The application was amended to Paragraph IV Certification, 8/13/96. The firm submitted documentation of receipt of notice by the innovator, 8/15-16/96. No indication of response by the innovator has been filed in the application.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Diltiazem
Hydrochloride USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

6/12/96	Original Submission.
8/13/96	Amendment - Paragraph IV Certification.
9/12/96	Amendment - Bioequivalence Telephone Amendment.
9/24/96	Amendment - Proof of Paragraph IV Notification Delivery.
11/11/96	Correspondence - Acknowledgement of Bioequivalence Letter of 8/31/96.
1/15/97	**Amendment - Response to Agency's letter of 12/27/96.**

FDA:

8/9/96	Receipt Acknowledged.
8/31/96	Issuance of Bioequivalence No Further Questions letter.
12/27/96	Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY
Calcium Channel Blocker

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

[redacted]

(b)4 - Confidential Business

)A).

(LoA).

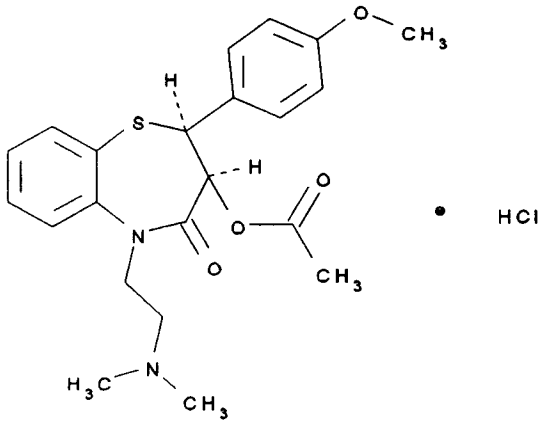
)A).

13. DOSAGE FORM
HG Capsule for oral administration

14. POTENCIES
60 mg, 90 mg, and 120 mg

15. CHEMICAL NAME AND STRUCTURE

Diltiazem Hydrochloride USP
$C_{22}H_{26}N_2O_4S.HCl$; M.W. = 450.99



(+)-5-[2-(Dimethylamino)ethyl]-*cis*-2,3-dihydro-3-hydroxy-2-(*p*-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one acetate (ester) monohydrochloride. CAS [33286-22-5]

Fine needles from ethanol-isopropanol, mp 207.5 - 212°C, optical rotation +98.3 ± 1.4° (c = 1.002 in methanol), 110 - 116 in a 1 to 100 solution in water. Freely soluble in water, methanol, chloroform: slightly soluble in absolute ethanol. Practically insoluble in benzene.

16. RECORDS AND REPORTS
9/17/96 - Labeling review, C. Hoppes.
10/28/96 - Bioequivalence review, M. Park.
11/26/96 - Chemistry review #1, G.J. Smith.
2/21/97 - Labeling review, J. White.

17. COMMENTS
The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

The Division of Bioequivalence found the drug product equivalent and granted waiver.

Acceptable EIR issued by the Office of Compliance.

Methods validation not required since drug substance and product are compendial.

The DMF for the drug substance was found satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved.

19. REVIEWER: Glen Jon Smith

DATE COMPLETED: February 13, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074910

BIOEQUIVALENCE REVIEW(S)

ANDA 74-910

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge road
P.O. BOX 4310
Morgantown WV 26504-4310

OCT 1 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Diltiazem Hydrochloride Extended-release Capsules 60 mg, 90 mg and 120 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following interim dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (Paddle) at 100 rpm. The test product should meet the following specifications:

4 hrs	(b)4 -
8 hrs	onfidenti
12 hrs	
24 hrs	Business

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

(b)4 -
Confidential

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Div. File

MAY - 5 1997

Diltiazem Hydrochloride ER Capsules	Mylan
60, 90 and 120 mg Capsules	Morgantown, WV
ANDA #74-910	Submission Date:
Reviewer: Moo Park	June 12, 1996
Filename: 74910add.497	September 12, 1996

Addendum to
Review of Two *In Vivo* Bioequivalence Studies, Dissolution Data and Two Waiver Requests

I. Objectives

Addendum was prepared to the original review dated October 28, 1996 to clarify the followings with regard to the steady-state study results:

1. Are the data in hard copy identical to the data in the submitted diskette?

2. Discrepancies found in the submission and reviewer's data summary recalculated by reviewer.

3. Subject #4 showed multiple missing plasma data points. If the subject is dropped from the statistical analyses, would the study still pass the 90% confidence intervals?

II. Summary of Findings

1. The data in the hard copy was found to be identical to the data in the diskette.

2. For the discrepancies found in the submission and reviewer's data summary recalculated by reviewer, Mylan ([redacted]) used wrong algorithm in determining CMAX. The CMAX was chosen from 96-180 hours instead of 168-180 hours interval, which was the last dosing interval in the steady-state study. As a result, the TMAX and Fluctuation also became wrong since the algorithm for the TMAX and Fluctuation involved CMAX. Reviewer's summary in the original review corrected all the wrong parameters. The insignificant discrepancies found in the mean plasma levels

in the submission and the reviewer's calculation is due to the missing values for subject #4. Reviewer calculated the mean plasma levels based on the interpolated data for missing values. The interpolation on linear scale for missing data may be used in AUC calculation. Mylan used the interpolation for AUC calculation. However, Mylan dropped the missing values in the calculation of mean plasma levels. Either way did not make any difference in the determination of bioequivalence.

3. The data analyses performed without the data for Subject #4 indicated that all the 90% confidence intervals for log trasformed AUCT, CMAX, CMIN and CAVG, calculated for diltiazem, desacetyl diltiazem and desmethyl diltiazem under steady-state conditions were within the acceptable range of 80-125%. Details of data analyses are given in Section IV.

IV. Results of Data Analyses without Subject #4

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under SS conditions

Table d1. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	89.58	26.68	97.45	31.20	0.92
1	86.13	35.18	88.23	27.07	0.98
2	82.14	32.80	84.68	26.93	0.97
3	88.41	38.64	87.10	27.01	1.02
4	103.84	51.03	94.87	29.41	1.09
5	123.15	53.23	113.72	34.63	1.08
6	155.16	57.18	149.64	40.14	1.04
7	160.66	54.65	161.17	38.27	1.00
8	154.48	46.80	160.10	37.55	0.96
9	136.04	45.30	146.87	32.65	0.93
10	120.08	40.04	130.13	34.58	0.92
11	104.56	42.43	112.31	31.31	0.93
12	93.16	39.20	99.16	32.58	0.94

b. PK parameters of diltiazem under SS conditions

Table d2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	1406.00	482.50	1427.11	355.09	0.99
CAVG	117.17	40.21	118.93	29.59	0.99
CMAX	170.17	52.85	171.22	36.84	0.99
CMIN	77.13	29.38	82.44	25.76	0.94
FLUC1	0.81	0.27	0.77	0.25	1.05
FLUC2	1.32	0.67	1.18	0.54	1.12
LAUCT	1340.60	0.31	1386.85	0.24	0.97
LCAVG	111.72	0.31	115.57	0.24	0.97
LCMAX	162.53	0.31	167.21	0.23	0.97
LCMIN	72.60	0.35	78.86	0.31	0.92
LFLUC1	0.77	0.34	0.74	0.31	1.04
LFLUC2	1.18	0.48	1.08	0.42	1.09

Table d3. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	1406.00	1427.11	0.99
CAVG	117.17	118.93	0.99
CMAX	170.17	171.22	0.99
CMIN	77.13	82.44	0.94
FLUC1	0.81	0.77	1.05
FLUC2	1.32	1.18	1.12
LAUCT	1340.60	1386.85	0.97
LCAVG	111.72	115.57	0.97
LCMAX	162.53	167.21	0.97
LCMIN	72.60	78.86	0.92
LFLUC1	0.77	0.74	1.04
LFLUC2	1.18	1.08	1.09

Table d4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	1406.00	1427.11	91.99	105.05
CAVG	117.17	118.93	91.99	105.05
CMAX	170.17	171.22	92.31	106.46
CMIN	77.13	82.44	86.92	100.18
FLUC1	0.81	0.77	94.90	115.26
FLUC2	1.32	1.18	96.71	127.66
LAUCT	1340.60	1386.85	90.78	102.94
LCAVG	111.72	115.57	90.78	102.94
LCMAX	162.53	167.21	90.26	104.68
LCMIN	72.60	78.86	85.80	98.78
LFLUC1	0.77	0.74	94.25	115.33
LFLUC2	1.18	1.08	94.85	126.34

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under SS conditions

Table dad1. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	14.94	15.27	17.49	18.59	0.85
1	14.96	15.89	17.19	19.29	0.87
2	14.73	14.38	16.95	19.22	0.87
3	15.12	16.04	16.90	19.90	0.89
4	15.75	17.79	17.24	20.26	0.91
5	16.65	17.41	17.64	19.48	0.94
6	17.93	19.22	18.51	20.52	0.97
7	19.24	20.65	20.03	22.65	0.96
8	19.38	20.81	20.98	23.62	0.92
9	19.23	19.16	21.49	23.75	0.89
10	18.83	20.70	20.62	23.63	0.91
11	17.22	19.52	20.02	25.87	0.86
12	16.96	19.89	18.90	24.36	0.90

b. PK parameters of desacetyl diltiazem under SS conditions

Table dad2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	205.00	218.54	225.79	259.34	0.91
CAVG	17.08	18.21	18.82	21.61	0.91
CMAX	20.33	21.09	22.30	25.21	0.91
CMIN	13.48	14.48	15.98	18.68	0.84
FLUC1	0.42	0.12	0.35	0.12	1.18
FLUC2	0.54	0.19	0.43	0.17	1.26
LAUCT	161.63	0.58	172.06	0.61	0.94
LCAVG	13.47	0.58	14.34	0.61	0.94
LCMAX	16.22	0.57	17.12	0.60	0.95
LCMIN	10.58	0.59	12.04	0.63	0.88
LFLUC1	0.40	0.31	0.33	0.37	1.20
LFLUC2	0.51	0.38	0.40	0.42	1.28

Table dad3. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	205.00	225.79	0.91
CAVG	17.08	18.82	0.91
CMAX	20.33	22.30	0.91
CMIN	13.48	15.98	0.84
FLUC1	0.42	0.35	1.18
FLUC2	0.54	0.43	1.26
LAUCT	161.63	172.06	0.94
LCAVG	13.47	14.34	0.94
LCMAX	16.22	17.12	0.95
LCMIN	10.58	12.04	0.88
LFLUC1	0.40	0.33	1.20
LFLUC2	0.51	0.40	1.28

Table dad4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	205.00	225.79	82.65	98.93
CAVG	17.08	18.82	82.65	98.93
CMAX	20.33	22.30	82.56	99.78
CMIN	13.48	15.98	73.59	95.13
FLUC1	0.42	0.35	105.53	130.56
FLUC2	0.54	0.43	111.14	141.78
LAUCT	161.63	172.06	89.00	99.16
LCAVG	13.47	14.34	89.00	99.16
LCMAX	16.22	17.12	89.34	100.48
LCMIN	10.58	12.04	83.05	92.85
LFLUC1	0.40	0.33	105.35	136.66
LFLUC2	0.51	0.40	110.14	149.60

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under SS conditions

Table dmd1. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	30.66	5.66	33.24	6.70	0.92
1	29.41	5.26	30.99	6.15	0.95
2	28.47	5.36	29.84	5.92	0.95
3	28.63	5.33	29.91	5.99	0.96
4	30.10	6.47	30.34	5.94	0.99
5	33.65	7.23	32.76	6.78	1.03
6	36.73	8.31	36.49	7.47	1.01
7	39.71	8.09	40.43	7.19	0.98
8	41.50	8.15	42.25	7.75	0.98
9	39.50	7.78	41.23	7.11	0.96
10	38.15	7.54	40.07	7.48	0.95
11	35.77	7.79	38.13	6.97	0.94
12	34.58	8.04	36.61	7.15	0.94

b. PK parameters of desmethyl diltiazem under SS conditions

Table dmd2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	414.24	76.96	427.37	77.07	0.97
CAVG	34.52	6.41	35.61	6.42	0.97
CMAX	42.37	7.92	43.38	7.43	0.98
CMIN	26.91	5.25	29.09	5.65	0.93
FLUC1	0.45	0.10	0.40	0.10	1.11
FLUC2	0.58	0.17	0.50	0.16	1.16
LAUCT	407.25	0.19	420.72	0.18	0.97
LCAVG	33.94	0.19	35.06	0.18	0.97
LCMAX	41.65	0.19	42.74	0.18	0.97
LCMIN	26.43	0.20	28.59	0.19	0.92
LFLUC1	0.44	0.24	0.39	0.26	1.11
LFLUC2	0.56	0.31	0.48	0.31	1.17

Table dmd3. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	414.24	427.37	0.97
CAVG	34.52	35.61	0.97
CMAX	42.37	43.38	0.98
CMIN	26.91	29.09	0.93
FLUC1	0.45	0.40	1.11
FLUC2	0.58	0.50	1.16
LAUCT	407.25	420.72	0.97
LCAVG	33.94	35.06	0.97
LCMAX	41.65	42.74	0.97
LCMIN	26.43	28.59	0.92
LFLUC1	0.44	0.39	1.11
LFLUC2	0.56	0.48	1.17

Table dmd4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	414.24	427.37	93.76	100.09
CAVG	34.52	35.61	93.76	100.09
CMAX	42.37	43.38	94.34	100.99
CMIN	26.91	29.09	88.51	96.52
FLUC1	0.45	0.40	101.02	120.73
FLUC2	0.58	0.50	103.81	128.86
LAUCT	407.25	420.72	93.64	100.07
LCAVG	33.94	35.06	93.64	100.07
LCMAX	41.65	42.74	93.75	101.32
LCMIN	26.43	28.59	88.66	96.40
LFLUC1	0.44	0.39	101.03	122.77
LFLUC2	0.56	0.48	103.42	131.49

V. Conclusion

This addendum clarified the data discrepancies between the submitted data and reviewer's calculation. The 90% confidence intervals for log trasformed AUCT, CMAX, CMIN and CAVG, calculated for the data without Subject #4 for diltiazem, desacetyl diltiazem and desmethyl diltiazem are within the acceptable range of 80-125%. This fully supports the conclusion made by reviewer in the original review dated October 28, 1996.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

/S/ 5/2/1997

RD INITIALED RMHATRE
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Concur: _____ Date: 5/2/97

Nicholas Fleischer, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-910 (original, duplicate), Park, Drug File, Division File

File history: Draft (4/30/97); Final (5/2/97)

OCT 28 1996

DW

Diltiazem Hydrochloride ER Capsules	Mylan
60, 90 and 120 mg Capsules	Morgantown, WV
ANDA #74-910	Submission Date:
Reviewer: Moo Park	June 12, 1996
Filename: 74910sdw.696	September 12, 1996

Review of Two *In Vivo* Bioequivalence Studies, Dissolution Data and Two Waiver Requests

I. Objectives

Review of:

- An open-label randomized, two-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem® SR, Hoechst Marion Roussel, 120 mg capsules under fasting and steady-state conditions. Fasting and steady-state studies were combined into one 8-day study.

- An open-label randomized, three-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem® SR, Hoechst Marion Roussel, 120 mg capsules under nonfasting conditions.

- Dissolution data for the 60 mg, 90 mg and 120 mg Capsules of the test and reference products.

- A waiver request for the 60 mg and 90 mg capsules of the test product.

II. Background

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of the cardiac and vascular smooth muscle.

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability of about 40%. Diltiazem undergoes extensive

metabolism, in which 2-4% of the unchanged drug appears in the urine. *In vitro* binding studies show that diltiazem is 70-80% bound to plasma proteins. The plasma elimination half-life following single or multiple drug administration is about 3-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem appear to bc in the range of 50-200 ng/mL. There is departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. Hepatic impairment delays elimination and increases half-life and bioavailability.

Diltiazem is absorbed from Cardizem^{R} SR dosage form to about 92% of a reference solution during steady-state dosing. A single 120 mg dose of the capsule results in detectable plasma levels within 2-3 hours and peak plasma levels at 6-11 hours. The apparent elimination half-life after single or multiple dosing is 5-7 hours. The departure from linearity similar to that observed with the conventional tablet is observed. As the dose of Cardizem^{R} SR is increased from 60 mg twice daily (BID) to 120 mg BID, there is an increase in the area under the plasma concentration-time curve (AUC) of 2.6 times. When the dose is increased from 240 to 360 mg daily, there is an increase in AUC of 1.8 times. The average plasma levels of the capsule dosed twice daily at steady-state are equivalent to the tablet dosed four times daily when the same total daily dose is administered.

Cardizem^{R} SR is indicated for the treatment of hypertension, at daily doses ranging from 120-360 mg/day. Doses of 60-120 mg BID are usual starting doses, while the usual optimum dosage range is 120-180 mg BID.

III. Study Details

Protocols of the two *in vivo* bioequivalence studies are summarized below:

A. **Fasting Single and Multiple Dose Study**

1. Protocol #9559

2. Applicant: Mylan, Morgantown, WV

3. Study sites:

   Clinical study: (b)4 - Confidential Business

   Analytical: Mylan Pharmaceuticals
   Morgantown, WV

4. Investigators:

Principal investigator: (b)4 - Confidential

5. Clinical study dates: 11/15-12/21/95

   Assay dates: 1/3-3/13/96

6. Study design: Open-label, randomized, two-way crossover design.

7. Subjects: Twenty-eight healthy male volunteers from the [redacted](b)4 - Confidential[redacted] area were accepted for entry into the clinical phase of the study. In accordance with the criteria noted in the protocol #9559, subjects were determined to be in good health prior to entry into the study on the basis of interview, physical examination, complete blood count, differential, clinical chemistries, and urinalysis. Four subjects were withdrawn during phase 1. Twenty-four subjects successfully completed both phases of the clinical portion of the study.

8. Product information:

   Treatment 1: Test product
   Diltiazem HCl ER Capsules, 120 mg
   Mylan Pharmaceuticals, Inc.
   Lot # 2B005L
   Manufacture Date: 10/25/95
   Production Lot: [redacted](b)4 -[redacted]

   Treatment 2: Reference product
   Cardizem® SR Capsules, 120 mg
   Hoechst Marion Roussel, Inc.
   Lot # P20228 - EXP. 2/96

9. Dosing: Each treatment consisted of the administration of a single 120 mg dose of extended release diltiazem HCl (1 x 120 mg capsules) on day 1, then a 120 mg dose every twelve hours for day 3 through day 7 and a single dose on the morning of day 8. Subjects engaged in normal activity for the first 12 hours following the morning dose, avoiding vigorous exertion and complete rest.

10. Food and fluid intake: Each dose was administered with 240 mL of water. Subjects were required to fast overnight and for five hours after each dose on study days 1 and 8. Standard meals were provided at five and ten hours after each dose. On days 3 through 7 subjects were given a standard breakfast one hour after dosing. Snacks were provided during the evening of each day. Water was not allowed from 2 hours before until 2 hours after the morning dosing but was allowed at all other

times. During housing, meal plans were identical for both periods.

11. Housing: Subjects were housed at the clinical site from 11 hours before the first dose until 24 hours after the first dose. For the dosing throughout days 3-8, volunteers entered the study site no later than 9:00 pm on the day prior to dosing and remain at the clinical site until 12 hours after dosing on day 8.

12. Washout period: 21 days.

13. Blood samples: Serial blood samples were collected for 48 hours after the first dose, and 12 hours after the last dose on day 8. Trough Cmin samples were taken prior to the morning dose on days 6, 7, and 8.

    Blood samples for single dose study: On day 1, a single-dose was administered and no other doses were given for 48 hours. Single-dose blood samples were taken pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, and 48 hours post dose.

    Blood samples for mulltiple dose study: Doses during the steady-state portion of the study were given at 12 hours on day 3 through day 7 and once in the morning on day 8. On days 5, 6, and 7, Cmin blood samples were collected at 96, 120, and 144 hours, respectively. On day 8 blood samples were collected at 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, and 180 hours after the first dose administered on day 1.

14. Monitoring of subjects: Vital signs (including blood pressure, pulse rates and a Lead 11 ECG) were measured pre-dose and hourly for the first 12 hours and then at 24, 36 and 48 hours post-dose during the single dose study. During steady-state attainment vital signs were measured before the morning dose at 96, 120, 144 and 168 hours, following the first dose of drug administration on day 1.

15. IRB and informed consent: Concurrence obtained.

16. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUCT, AUCI, CMAX, KE, THALF, CAVG, CMIN, TMAX, FLUC1, FLUC2 and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUCT, AUCI, CMAX, CAVG, CMIN, FLUC1, AND FLUC2. An analysis of steady-state attainment was performed using concentration data from the 120, 144 and 168 hour plasma samples.

B. Bioequivalence Study under Nonfasting Conditions

1. Protocol #9572

2. Applicant: Mylan, Morgantown, WV

3. Study sites:

Clinical study: (b)4 - Confidential Business h

Analytical: Mylan Pharmaceuticals
Morgantown, WV

4. Investigators:

Principal investigator: (b)4 - Confidential

5. Clinical study dates: 1/14-2/13/96

Assay dates: 2/14-3/7/96

6. Study design: Open-label, randomized, three-way crossover design.

7. Subjects: Twenty-three healthy male volunteers from the (b)4 - Confidential area were accepted for entry into the clinical phase of the study. In accordance with the criteria noted in the protocol #9572, subjects were determined to be in good health prior to entry into the study on the basis of interview, physical examination, complete blood count, differential, clinical chemistries, and urinalysis.

Twenty volunteers were present on the first day of dosing. Subjects #8 and #6 failed to report for personal reasons prior to phase 2 and 3. Subject #17 was withdrawn due to treatment for bronchitis and Subject #20 was discontinued due to pharyngitis prior to phase 2 and 3, respectively. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

8. Product information:

Treatment 1:
Diltiazem HCl ER Capsules, 120 mg
Mylan Pharmaceuticals Inc.
1 x 120 ms, Administered with Food
Lot #2B005L
Production Lot - (b)4 Units
Manufacturing date - 10/25/95

Treatment 2:
Cardizem® SR Capsules, 120 mg
Marion Merrell Dow
1 x 120 mg, Administered with food
Lot #P20228, Exp. 2/96

Treatment 3:
Diltiazem HCl ER Capsules, 120 mg
Mylan Pharmaceuticals Inc.
1 x 120 mg, Fasting Administration
Lot #2B005L, Exp. To Be Determined
Production Lot - (b)4 - Units
Manufacturing Date- 10/25/95

9. Dosing: Each treatment consisted of the administration of 120 mg of the extended release diltiazem HCl (1 x 120 mg capsule) with 240 mL of water.

10. Food and fluid intake: Subjects receiving treatments 1 and 2 (fed) were required to fast overnight until 15 minutes prior to dosing, when they were given a standard breakfast. Breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 serving of hashed brown potatoes, 6 ounces of orange juice, and 8 ounces of whole milk. Standard meals (lunch and dinner) were provided at approximately 5 and 10 hours after dosing, and at appropriate times thereafter. Water was not permitted from two hours before until two hours after dosing, but was allowed at all other times.

11. Housing: From evening on the day prior to dosing until 24 hours after dosing.

12. Washout period: 14 days.

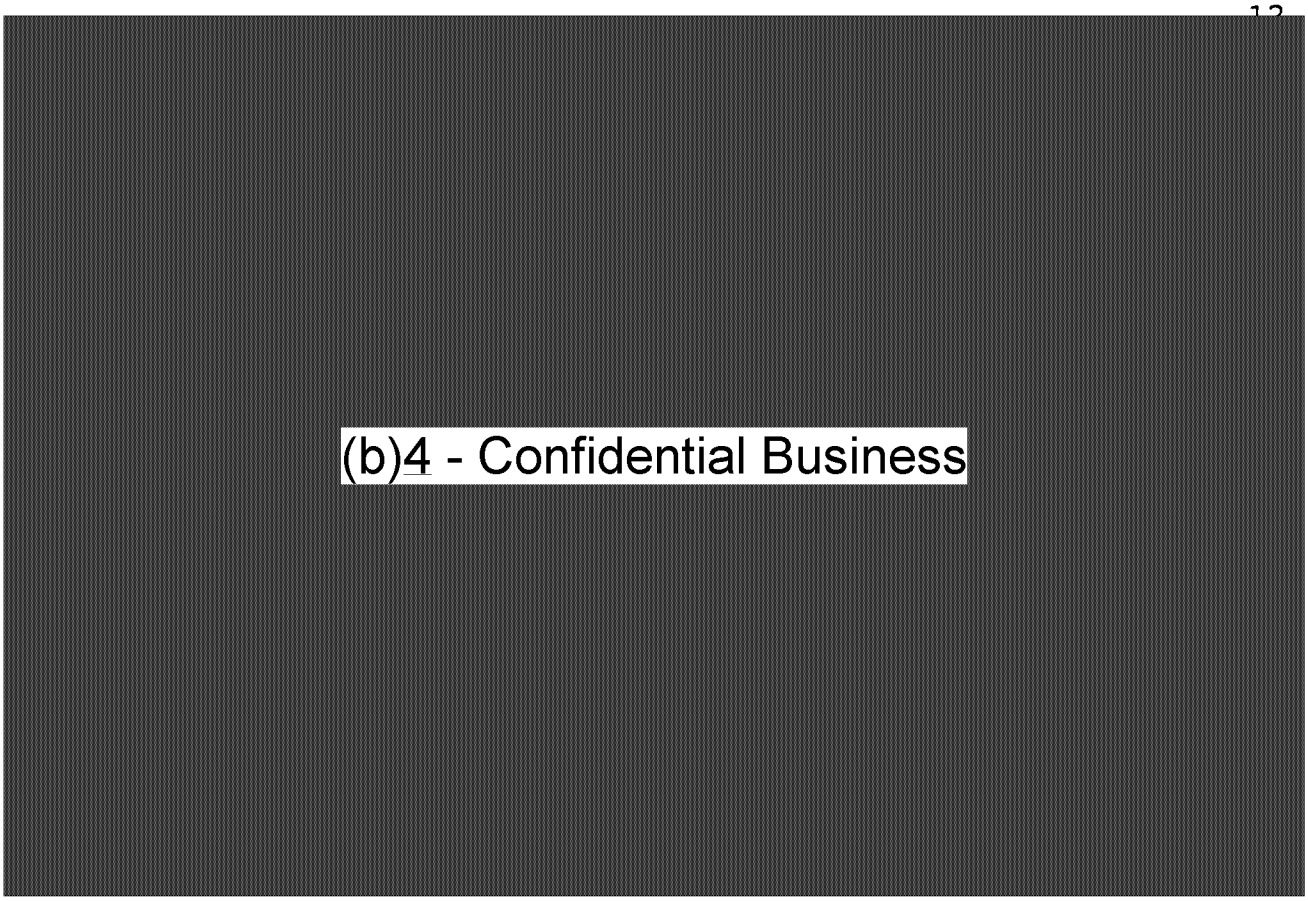
13. Blood samples: Serial blood samples were collected predose, and then post dose at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 24, 30, 36 and 48 hours.

14. Monitoring of subjects: Volunteers engaged in normal activity for the first 12 hours after drug administration. Vital signs (including blood pressure, and pulse rate) were measured predose and hourly for the first 12 hours and then at 16, 24, 36 and 48 hours after dosing. A lead 11 ECG was recorded prior to dosing and hourly for the first 12 hours then at 24, 36 and 48 hours after dosing.

15. IRB and informed consent: Concurrence obtained.

16. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUCT, AUCI, CMAX, KE, THALF, TMAX, and blood levels at each sampling points. Test/Reference ratios were calculated for AUCT, AUCI, and CMAX.

IV. Validation of Assay Method for Plasma Samples



V. In Vivo Results with Statistical Analysis

A. Single Dose Study under Fasting Conditions and Multiple Dose Study under Steady-State Conditions (#9559)

Twenty-eight healthy male volunteers were accepted for entry into the clinical phase of the study. Four subjects were withdrawn during phase 1. Subject #28 was withdrawn due to adverse events assessed as probably drug related. Subjects #3 and #27 were withdrawn due to protocol violations. Subject #8 elected to withdraw from the study for personal reasons not related to the study. Twenty-four subjects successfully completed both phases of the clinical portion of the study. Subject #13 was removed from the statistical portion of the study due to a protocol violation. This individual took an over-the-counter medication during the washout phase of the study. Therefore, the pharmacokinetic and statistical analyses were performed on the data for 23 subjects.

Vital signs were analyzed for statistical differences; these include systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval. There were no clinically significant differences in the parameters evaluated.

There were eight adverse events (7 subjects) reported during the eight day study. There were seven reports of headache and one

experience of dizziness, which were all assessed as probably drug related. There were no serious or life-threatening medical events reported for this study.

A-1. Single Dose Study Results under Fasting Conditions

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products were similar to each other as shown in Fig. 1 and Table 10. Peak mean diltiazem levels for the test and reference products were 81 ng/mL at 7 hours and 83 ng/mL at 7 hours, respectively. The peak diltiazem levels are approximately 12-13 times higher than those of desacetyl diltiazem and 4 times higher than those of desmethyl diltiazem.

The plasma data show that there is an apparent time lag of two hours in absorption process after the dose is administered under fasting conditions.

Table 10. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST(LOT#2B005L); MEAN2=REFERENCE(LOT#P20228)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.10	0.50	0.00
2	1.42	2.26	2.52	1.78	0.56
3	9.76	9.53	7.36	3.38	1.33
4	22.91	26.57	16.98	12.94	1.35
5	43.35	34.90	36.09	23.34	1.20
6	74.35	38.42	76.26	31.87	0.98
7	81.19	36.12	82.57	22.50	0.98
8	77.95	29.41	82.05	18.46	0.95
9	72.68	26.22	79.13	18.04	0.92
10	63.86	20.73	68.18	14.99	0.94
11	57.29	17.21	60.30	13.54	0.95
12	49.77	15.63	51.28	11.78	0.97
16	28.57	10.45	28.01	8.24	1.02
24	11.70	4.87	11.48	4.46	1.02
36	1.81	1.74	2.03	2.20	0.89
48	0.10	0.46	0.09	0.43	1.07

b. PK parameters of diltiazem under fasting conditions

Arithmetic and geometric means are summarized in Table 11 and least-squares means are shown in Table 12. The test/reference ratios of the least-squares means for the log-transformed PK

parameters, LAUCT, LAUCI, and LCMAX, are within 0.92-0.96 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 13.

Table 11. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	950.99	349.26	954.35	215.36	1.00
AUCT	909.53	356.72	910.99	221.50	1.00
CMAX	88.53	33.01	93.14	26.64	0.95
KE	0.12	0.02	0.13	0.02	0.98
LAUCI	891.99	0.37	928.76	0.25	0.96
LAUCT	845.03	0.40	883.06	0.26	0.96
LCMAX	82.70	0.38	89.89	0.27	0.92
THALF	5.69	0.92	5.54	0.78	1.03
TMAX	7.52	1.68	7.48	1.41	1.01

Table 12. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCI	947.58	953.24	0.99
AUCT	906.33	910.61	1.00
CMAX	88.23	92.89	0.95
LAUCI	888.78	927.18	0.96
LAUCT	842.04	882.13	0.95
LCMAX	82.41	89.55	0.92

Table 13. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	947.58	953.24	90.46	108.35
AUCT	906.33	910.61	89.72	109.35
CMAX	88.23	92.89	82.53	107.44
LAUCI	888.78	927.18	87.08	105.53
LAUCT	842.04	882.13	85.74	106.28
LCMAX	82.41	89.55	81.29	104.17

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products were similar to each other as shown in Fig. 2 and Table 14. Peak mean desacetyl diltiazem levels for the test and reference products were 6.2 ng/mL at 10 hours and 6.8 ng/mL at 10 hours, respectively.

Table 14. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.00	0.00	0.00	0.00	.
3	0.05	0.23	0.00	0.00	.
4	0.78	1.96	0.29	0.69	2.73
5	1.74	1.42	1.50	1.52	1.15
6	3.61	1.66	3.97	2.21	0.91
7	4.61	1.85	5.25	2.46	0.88
8	5.54	2.30	6.18	2.75	0.90
9	5.97	2.54	6.67	3.09	0.89
10	6.19	2.92	6.83	3.48	0.91
11	6.15	3.26	6.79	3.99	0.91
12	5.86	3.44	6.35	3.84	0.92
16	5.02	4.06	5.30	4.11	0.95
24	3.03	3.79	3.06	2.71	0.99
36	0.88	2.62	0.63	1.50	1.41
48	0.33	1.13	0.20	0.66	1.68

b. PK parameters of desacetyl diltiazem under fasting conditions

Arithmetic and geometric means are summarized in Table 15 and least-squares means are shown in Table 16. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within 0.90-0.95 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 17.

Table 15. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	147.79	134.40	147.03	105.15	1.01
AUCT	111.03	117.88	112.44	100.87	0.99
CMAX	7.13	3.89	7.39	3.95	0.97
KE	0.07	0.02	0.07	0.02	1.03
LAUCI	117.79	0.62	127.21	0.49	0.93
LAUCT	82.68	0.70	92.23	0.56	0.90
LCMAX	6.38	0.46	6.72	0.42	0.95
THALF	10.40	2.86	10.49	2.39	0.99
TMAX	9.74	2.20	9.83	1.40	0.99

Table 16. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCI	149.22	148.16	1.01
AUCT	112.47	113.71	0.99
CMAX	7.17	7.42	0.97
LAUCI	118.16	127.74	0.93
LAUCT	83.11	92.75	0.90
LCMAX	6.40	6.72	0.95

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCI	149.22	148.16	88.99	112.43
AUCT	112.47	113.71	88.32	109.50
CMAX	7.17	7.42	87.40	106.02
LAUCI	118.16	127.74	82.78	103.36
LAUCT	83.11	92.75	80.14	100.20
LCMAX	6.40	6.72	87.22	103.95

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products

were similar to each other as shown in Fig. 3 and Table 18. Peak mean desmethyl diltiazem levels for the test and reference products were 19.8 ng/mL at 9 hours and 21.5 ng/mL at 9 hours, respectively.

Table 18. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.00	0.00	0.09	0.44	0.00
3	1.45	1.78	1.40	1.44	1.03
4	4.90	3.09	4.60	2.56	1.06
5	9.69	4.39	8.95	4.95	1.08
6	15.40	5.11	16.00	6.15	0.96
7	18.58	5.65	19.44	5.24	0.96
8	19.62	5.06	20.72	3.89	0.95
9	19.75	4.61	21.52	4.09	0.92
10	19.26	4.26	20.91	3.63	0.92
11	18.92	4.02	19.99	3.29	0.95
12	17.97	3.85	18.84	3.22	0.95
16	13.65	3.41	13.96	2.80	0.98
24	7.57	2.34	7.65	1.90	0.99
36	2.26	1.73	2.23	1.76	1.01
48	0.11	0.53	0.09	0.44	1.20

b. <u>PK parameters of desmethyl diltiazem under fasting conditions</u>

Arithmetic and geometric means are summarized in Table 19 and least-squares means are shown in Table 20. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within 0.94-0.96 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 21.

Table 19. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	383.35	92.77	394.57	75.02	0.97
AUCT	335.96	94.43	345.41	76.31	0.97
CMAX	21.38	4.46	22.75	4.54	0.94
KE	0.08	0.01	0.08	0.01	0.98
LAUCI	372.49	0.25	387.22	0.20	0.96
LAUCT	323.15	0.29	336.79	0.24	0.96
LCMAX	20.96	0.20	22.32	0.20	0.94
THALF	8.74	1.10	8.71	1.63	1.00
TMAX	9.09	1.83	8.70	1.46	1.05

Table 20. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCI	382.58	394.39	0.97
AUCT	335.46	345.46	0.97
CMAX	21.32	22.70	0.94
LAUCI	371.52	386.85	0.96
LAUCT	322.46	336.71	0.96
LCMAX	20.90	22.27	0.94

Table 21. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	382.58	394.39	91.40	102.61
AUCT	335.46	345.46	89.96	104.25
CMAX	21.32	22.70	87.30	100.54
LAUCI	371.52	386.85	90.26	102.19
LAUCT	322.46	336.71	88.70	103.41
LCMAX	20.90	22.27	87.89	100.28

A-2. Study Results under Steady-State (SS) Conditions

The applicant showed by regression analysis and t-test that steady-state was achieved within 5 days of dosing. The applicant also showed that no statistically significant differences in mean slopes between treatments exist for diltiazem, desacetyl diltiazem or N-desmethyl diltiazem.

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 4 and Table 22. Peak mean diltiazem levels for the test and reference products were 157 ng/mL at 7 hours and 159 ng/mL at 7 hours, respectively. The peak diltiazem levels are approximately 8 times higher than those of desacetyl diltiazem and 4 times higher than those of desmethyl diltiazem.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 22. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	88.43	26.65	95.36	32.09	0.93
1	84.54	35.21	86.22	28.15	0.98
2	80.67	32.81	82.51	28.29	0.98
3	86.64	38.69	85.04	28.17	1.02
4	101.37	51.24	92.70	30.56	1.09
5	119.82	54.41	111.53	35.42	1.07
6	150.93	59.42	146.69	41.69	1.03
7	156.69	56.69	158.53	39.49	0.99
8	151.27	48.24	158.52	37.46	0.95
9	134.13	45.20	144.93	33.23	0.93
10	117.53	40.99	128.07	35.19	0.92
11	101.35	44.22	110.18	32.25	0.92
12	89.11	42.94	94.85	37.96	0.94

b. PK parameters of diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 23 and least-squares means are shown in Table 24. The test/reference

ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within 0.92-1.04 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within the acceptable range of 80-125 as shown in Table 25.

Table 23. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	1367.69	505.94	1398.65	372.81	0.98
CAVG	113.97	42.16	116.55	31.07	0.98
CMAX	166.77	54.14	169.16	37.34	0.99
CMIN	73.78	32.90	78.86	30.48	0.94
FLUC1	0.87	0.38	0.82	0.34	1.06
FLUC2	1.32	0.67	1.18	0.54	1.12
LAUCT	1287.05	0.36	1352.01	0.27	0.95
LCAVG	107.25	0.36	112.67	0.27	0.95
LCMAX	158.57	0.33	165.03	0.23	0.96
LCMIN	72.60	0.35	78.86	0.31	0.92
LFLUC1	0.80	0.40	0.77	0.37	1.04
LFLUC2	1.18	0.48	1.08	0.42	1.09

Table 24. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	1363.27	1396.96	0.98
CAVG	113.61	116.41	0.98
CMAX	166.35	168.72	0.99
CMIN	73.60	78.79	0.93
FLUC1	0.86	0.82	1.06
FLUC2	1.32	1.18	1.12
LAUCT	1284.82	1351.40	0.95
LCAVG	107.07	112.62	0.95
LCMAX	158.23	164.61	0.96
LCMIN	72.60	78.86	0.92
LFLUC1	0.80	0.76	1.05
LFLUC2	1.18	1.08	1.09

Table 25. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	1363.27	1396.96	91.03	104.15
CAVG	113.61	116.41	91.03	104.15
CMAX	166.35	168.72	91.61	105.58
CMIN	73.60	78.79	86.80	100.03
FLUC1	0.86	0.82	96.50	115.22
FLUC2	1.32	1.18	96.71	127.66
LAUCT	1284.82	1351.40	88.92	101.66
LCAVG	107.07	112.62	88.92	101.66
LCMAX	158.23	164.61	89.32	103.45
LCMIN	72.60	78.86	85.80	98.78
LFLUC1	0.80	0.76	95.05	115.28
LFLUC2	1.18	1.08	94.85	126.34

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 5 and Table 26. Peak mean desacetyl diltiazem levels for the test and reference products were 18.9 ng/mL at 8 hours and 21.1 ng/mL at 9 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 26. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	14.66	14.98	17.16	18.23	0.85
1	14.63	15.60	16.84	18.92	0.87
2	14.40	14.14	16.53	18.88	0.87
3	14.75	15.77	16.49	19.54	0.89
4	15.33	17.50	16.81	19.90	0.91
5	16.17	17.17	17.24	19.14	0.94
6	17.42	18.93	18.10	20.14	0.96
7	18.70	20.34	19.60	22.23	0.95
8	18.86	20.49	20.54	23.17	0.92
9	18.75	18.86	21.09	23.29	0.89
10	18.25	20.41	20.06	23.25	0.91
11	16.59	19.31	19.28	25.53	0.86
12	16.23	19.76	18.07	24.13	0.90

b. PK parameters of desacetyl diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 27 and least-squares means are shown in Table 28. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within 0.88-1.19 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, and LCMIN are within the acceptable range of 80-125 as shown in Table 29. The 90% confidence interval for LFLUC1 was 105-135.

Table 27. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	199.23	215.30	220.14	254.82	0.91
CAVG	16.60	17.94	18.34	21.24	0.91
CMAX	19.82	20.75	21.87	24.72	0.91
CMIN	12.89	14.42	15.28	18.55	0.84
FLUC1	0.46	0.24	0.41	0.27	1.14
FLUC2	0.54	0.19	0.43	0.17	1.26
LAUCT	156.08	0.59	167.74	0.61	0.93
LCAVG	13.01	0.59	13.98	0.61	0.93
LCMAX	15.77	0.57	16.87	0.59	0.93
LCMIN	10.58	0.59	12.04	0.63	0.88
LFLUC1	0.42	0.40	0.36	0.48	1.19
LFLUC2	0.51	0.38	0.40	0.42	1.28

Table 28. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	201.91	223.32	0.90
CAVG	16.83	18.61	0.90
CMAX	20.07	22.16	0.91
CMIN	13.09	15.53	0.84
FLUC1	0.46	0.40	1.14
FLUC2	0.54	0.43	1.26
LAUCT	157.19	168.90	0.93
LCAVG	13.10	14.08	0.93
LCMAX	15.88	16.96	0.94
LCMIN	10.58	12.04	0.88
LFLUC1	0.42	0.35	1.19
LFLUC2	0.51	0.40	1.28

Table 29. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	201.91	223.32	82.55	98.27
CAVG	16.83	18.61	82.55	98.27
CMAX	20.07	22.16	82.30	98.92
CMIN	13.09	15.53	73.69	94.85
FLUC1	0.46	0.40	103.43	125.26
FLUC2	0.54	0.43	111.14	141.78
LAUCT	157.19	168.90	88.16	98.25
LCAVG	13.10	14.08	88.16	98.25
LCMAX	15.88	16.96	88.16	99.41
LCMIN	10.58	12.04	83.05	92.85
LFLUC1	0.42	0.35	105.29	135.06
LFLUC2	0.51	0.40	110.14	149.60

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 6 and Table 30. Peak mean desmethyl diltiazem levels for the test and reference products were 40.7 ng/mL at 8 hours and 42.0 ng/mL at 8 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 30. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	30.47	5.61	32.89	6.76	0.93
1	28.96	5.59	30.61	6.28	0.95
2	28.06	5.58	29.31	6.31	0.96
3	28.18	5.65	29.42	6.30	0.96
4	29.53	6.88	29.87	6.21	0.99
5	32.88	7.97	32.34	6.93	1.02
6	35.92	9.00	36.06	7.59	1.00
7	38.86	8.88	39.98	7.36	0.97
8	40.67	8.90	42.03	7.64	0.97
9	38.85	8.22	40.88	7.16	0.95
10	37.21	8.65	39.57	7.69	0.94
11	34.57	9.54	37.52	7.42	0.92
12	33.07	10.66	35.02	10.34	0.94

b. PK parameters of desmethyl diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 31 and least-squares means are shown in Table 32. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within 0.92-1.11 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, and LCMIN are within the acceptable range of 80-125 as shown in Table 33.

Table 31. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	403.86	90.17	421.01	81.23	0.96
CAVG	33.66	7.51	35.08	6.77	0.96
CMAX	41.83	8.17	43.26	7.28	0.97
CMIN	25.74	7.60	27.83	8.20	0.93
FLUC1	0.52	0.35	0.46	0.27	1.12
FLUC2	0.58	0.17	0.51	0.16	1.15
LAUCT	392.62	0.26	413.41	0.20	0.95
LCAVG	32.72	0.26	34.45	0.20	0.95
LCMAX	41.05	0.20	42.64	0.18	0.96
LCMIN	26.43	0.20	28.59	0.19	0.92
LFLUC1	0.47	0.40	0.42	0.39	1.11
LFLUC2	0.56	0.31	0.49	0.31	1.15

Table 32. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	403.33	420.72	0.96
CAVG	33.61	35.06	0.96
CMAX	41.75	43.20	0.97
CMIN	25.75	27.85	0.92
FLUC1	0.51	0.46	1.12
FLUC2	0.58	0.51	1.15
LAUCT	392.23	413.08	0.95
LCAVG	32.69	34.42	0.95
LCMAX	40.97	42.58	0.96
LCMIN	26.43	28.59	0.92
LFLUC1	0.46	0.42	1.11
LFLUC2	0.56	0.49	1.15

Table 33. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	403.33	420.72	92.30	99.43
CAVG	33.61	35.06	92.30	99.43
CMAX	41.75	43.20	93.26	100.00
CMIN	25.75	27.85	88.45	96.48
LAUCT	392.23	413.08	90.59	99.52
LCAVG	32.69	34.42	90.59	99.52
LCMAX	40.97	42.58	92.47	100.13
LCMIN	26.43	28.59	88.66	96.40

B. Study under Nonfasting Conditions (#9572)

Twenty-three healthy male volunteers were accepted for entry into the clinical phase of the study. Twenty volunteers were present on the first day of dosing. Subjects #8 and #6 failed to report for personal reasons which were not study related prior to phase 2 and 3, respectively. Subject #17 was withdrawn due to treatment for bronchitis and Subject #20 was discontinued due to pharyngitis prior to phase 2 and 3, respectively. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

Vital signs (including blood pressure, and pulse rate) were measured predose and hourly for the first 12 hours and then at 16, 24, 36 and 48 hours after dosing. A lead 11 ECG was recorded prior to dosing and hourly for the first 12 hours then at 24, 36 and 48 hours after dosing. There were no clinically significant differences in the vital signs for the fed treatments (1 and 2).

There were twelve adverse events reported for this study. Of the twelve reported, eleven were assessed as drug-related. There were ten reports of a headache and one report of blurred vision. Prior to phase 3 subject #20 was discontinued due to pharyngitis. There were no serious or life threatening adverse events reported for this study.

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products

under nonfasting conditions were similar to each other as shown in Fig. 7 and Table 34. Mean plasma level-time profile for the test product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean diltiazem levels for the test-fed, reference-fed, and test-fast were 81.6 ng/mL at 8 hours, 80.6 ng/mL at 8 hours, and 83.3 ng/mL at 7 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under fasting and nonfasting conditions.

Table 34. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FED; MEAN2=REFERENCE-FED; MEAN3=TEST-FAST
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.71	2.10	2.17	2.84	1.70	1.88
3	5.27	5.40	7.46	5.29	7.52	5.88
4	16.18	10.08	14.78	10.96	20.44	15.79
5	27.40	21.10	21.66	15.26	41.38	33.04
6	55.25	31.96	46.52	20.06	79.73	44.96
7	69.61	31.34	63.57	22.95	83.31	38.75
8	81.58	33.64	80.59	34.77	81.11	40.85
9	76.93	29.25	76.11	29.54	75.06	40.28
10	69.53	27.17	73.28	30.56	66.42	37.78
11	57.58	23.93	66.73	29.75	54.84	28.93
12	49.23	23.39	57.75	26.13	46.48	25.13
14	36.46	17.89	43.92	21.85	36.12	18.80
16	27.42	14.63	32.03	18.14	26.74	14.37
18	21.74	13.17	22.70	11.90	20.41	11.98
24	11.87	8.54	12.64	7.32	11.22	6.92
30	6.10	5.06	6.33	4.91	5.69	4.65
36	2.80	3.41	2.57	2.64	2.60	2.35
48	0.39	1.08	0.88	1.38	0.48	1.03

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	0.33	0.42	1.28
3	0.71	0.70	0.99
4	1.09	0.79	0.72
5	1.26	0.66	0.52
6	1.19	0.69	0.58
7	1.10	0.84	0.76
8	1.01	1.01	0.99
9	1.01	1.02	1.01
10	0.95	1.05	1.10
11	0.86	1.05	1.22
12	0.85	1.06	1.24
14	0.83	1.01	1.22
16	0.86	1.03	1.20
18	0.96	1.06	1.11
24	0.94	1.06	1.13
30	0.96	1.07	1.11
36	1.09	1.08	0.99
48	0.45	0.82	1.83

b. <u>PK parameters of diltiazem under nonfasting conditions</u>

Arithmetic and geometric means are summarized in Table 35 and least-squares means are shown in Table 36. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within 0.95-1.07 range.

Table 35. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	902.02	389.59	949.24	429.26	931.91	490.88
AUCT	869.53	389.00	913.30	430.48	903.22	490.27
CMAX	92.31	30.41	88.66	35.01	90.98	44.80
KE	0.12	0.03	0.11	0.03	0.11	0.02
LAUCI	826.43	0.43	873.67	0.41	808.06	0.57
LAUCT	791.47	0.45	833.98	0.43	775.15	0.59
LCMAX	88.31	0.30	83.43	0.35	79.64	0.56
THALF	6.22	1.51	7.01	2.54	6.29	1.28
TMAX	8.13	1.67	9.25	1.44	7.38	1.02

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	0.95	0.97	1.02
AUCT	0.95	0.96	1.01
CMAX	1.04	1.01	0.97
KE	1.09	1.04	0.95
LAUCI	0.95	1.02	1.08
LAUCT	0.95	1.02	1.08
LCMAX	1.06	1.11	1.05
THALF	0.89	0.99	1.11
TMAX	0.88	1.10	1.25

Table 36. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	922.64	964.77	952.53	0.96	0.97	1.01
AUCT	890.24	928.21	923.94	0.96	0.96	1.00
CMAX	93.14	88.03	91.82	1.06	1.01	0.96
LAUCI	838.64	882.67	819.99	0.95	1.02	1.08
LAUCT	803.78	842.49	787.21	0.95	1.02	1.07
LCMAX	88.90	82.90	80.18	1.07	1.11	1.03

2. Desacetyl Diltiazem

a. Plasma levels of desacetyl diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products under nonfasting conditions were similar to each other as shown in Fig. 8 and Table 37. Mean plasma level-time profile for the test

product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean desacetyl diltiazem levels for the test-fed, reference-fed, and test-fast were 6.9 ng/mL at 10 hours, 6.4 ng/mL at 12 hours, and 6.5 ng/mL at 9 hours, respectively.

Table 37. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00
4	0.31	0.56	0.22	0.62	0.44	0.80
5	1.00	1.20	0.65	1.05	1.52	1.81
6	2.69	1.83	2.18	1.24	3.81	2.62
7	4.20	2.59	3.52	1.74	5.04	2.47
8	5.47	2.89	4.97	2.13	5.65	2.85
9	6.61	3.32	5.98	2.70	6.49	3.25
10	6.85	3.64	6.21	2.83	6.34	3.83
11	6.58	3.75	6.35	3.30	6.41	3.58
12	6.51	3.72	6.38	3.42	6.14	3.73
14	5.91	3.33	6.03	3.41	5.81	3.37
16	5.34	3.01	5.50	3.44	5.15	2.99
18	4.51	2.84	4.62	2.80	4.27	2.71
24	3.25	2.39	3.27	2.28	3.07	2.11
30	1.84	1.86	1.77	1.98	1.60	1.80
36	0.71	1.38	0.77	1.17	0.74	1.09
48	0.21	0.60	0.18	0.49	0.15	0.42

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	.	.	.
3	.	.	.
4	1.41	0.71	0.51
5	1.54	0.66	0.43
6	1.24	0.71	0.57
7	1.20	0.83	0.70
8	1.10	0.97	0.88
9	1.11	1.02	0.92
10	1.10	1.08	0.98
11	1.04	1.03	0.99
12	1.02	1.06	1.04
14	0.98	1.02	1.04
16	0.97	1.04	1.07
18	0.98	1.06	1.08
24	0.99	1.06	1.06
30	1.04	1.15	1.11
36	0.92	0.95	1.03
48	1.17	1.35	1.16

b. PK parameters of desacetyl diltiazem under nonfasting conditions

Arithmetic and geometric means are summarized in Table 38 and least-squares means are shown in Table 39. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within 1.0-1.1 range.

Table 38. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCI	162.22	103.64	140.45	82.43	148.46	82.40
AUCT	117.65	84.82	114.15	79.55	114.47	79.86
CMAX	7.40	3.80	7.08	3.34	6.95	3.64
KE	0.06	0.04	0.06	0.02	0.06	0.03
LAUCI	133.42	0.67	121.41	0.55	128.79	0.56
LAUCT	92.85	0.73	93.01	0.66	89.77	0.77
LCMAX	6.56	0.51	6.46	0.43	6.11	0.54
THALF	15.15	15.28	11.75	3.24	12.03	5.76
TMAX	10.19	2.07	10.81	1.76	10.13	1.96

(CONTINUED)

PARAMETER	RMEAN12	RMEAN13	RMEAN23
AUCI	1.16	1.09	0.95
AUCT	1.03	1.03	1.00
CMAX	1.05	1.06	1.02
KE	1.01	1.02	1.01
LAUCI	1.10	1.04	0.94
LAUCT	1.00	1.03	1.04
LCMAX	1.01	1.07	1.06
THALF	1.29	1.26	0.98
TMAX	0.94	1.01	1.07

Table 39. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	161.40	144.71	145.85	1.12	1.11	0.99
AUCT	119.18	117.17	116.00	1.02	1.03	1.01
CMAX	7.41	7.18	6.96	1.03	1.06	1.03
LAUCI	131.03	124.13	125.11	1.06	1.05	0.99
LAUCT	92.61	94.50	89.53	0.98	1.03	1.06
LCMAX	6.51	6.53	6.07	1.00	1.07	1.08

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products under nonfasting conditions were similar to each other as shown in Fig. 9 and Table 40. Mean plasma level-time profile for the test product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean desmethyl diltiazem levels for the test-fed, reference-fed, and test-fast were 21.9 ng/mL at 9 hours, 21.3 ng/mL at 10 hours, and 19.8 ng/mL at 9 hours, respectively.

Table 40. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00
3	0.35	1.00	0.58	1.30	1.08	1.47
4	3.77	2.76	3.38	1.85	4.08	2.60
5	6.97	4.07	5.61	2.08	8.36	4.67
6	14.20	5.95	12.54	3.27	15.80	5.93
7	18.03	6.32	16.82	3.29	18.85	5.81
8	21.66	5.33	20.41	3.97	19.81	5.99
9	21.87	4.50	20.84	4.46	19.83	6.42
10	21.51	4.35	21.32	5.44	19.17	6.20
11	19.78	4.50	20.70	5.44	18.07	5.86
12	18.72	4.73	19.49	5.39	16.59	5.72
14	15.71	4.23	17.29	5.07	15.03	4.80
16	13.35	3.95	14.56	4.99	12.65	4.11
18	11.37	3.93	11.90	3.90	10.53	3.74
24	7.41	3.17	7.69	3.09	6.90	3.09
30	4.72	2.91	5.21	2.54	4.26	2.84
36	2.29	2.14	2.33	2.15	2.00	2.00
48	0.32	0.89	0.32	0.89	0.27	0.74

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	.	.	.
3	0.61	0.33	0.54
4	1.11	0.93	0.83
5	1.24	0.83	0.67
6	1.13	0.90	0.79
7	1.07	0.96	0.89
8	1.06	1.09	1.03
9	1.05	1.10	1.05
10	1.01	1.12	1.11
11	0.96	1.09	1.15
12	0.96	1.13	1.17
14	0.91	1.05	1.15
16	0.92	1.06	1.15
18	0.96	1.08	1.13
24	0.96	1.07	1.12
30	0.91	1.11	1.22
36	0.98	1.14	1.16
48	0.99	1.18	1.19

b. <u>PK parameters of desmethyl diltiazem under nonfasting conditions</u>

Arithmetic and geometric means are summarized in Table 41 and least-squares means are shown in Table 42. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within 0.98-1.04 range.

Table 41. ARITHMETIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	377.32	114.56	387.30	120.10	357.15	128.32
AUCT	342.54	110.55	350.29	116.94	321.45	127.27
CMAX	23.68	4.11	23.15	5.22	21.17	6.64
KE	0.09	0.01	0.08	0.01	0.09	0.01
LAUCI	360.60	0.32	370.38	0.31	335.17	0.37
LAUCT	325.40	0.34	332.91	0.33	297.28	0.42
LCMAX	23.34	0.18	22.64	0.22	20.20	0.32
THALF	8.10	1.21	8.53	1.34	8.29	1.20
TMAX	8.69	1.45	9.31	1.35	8.19	1.17

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	0.97	1.06	1.08
AUCT	0.98	1.07	1.09
CMAX	1.02	1.12	1.09
KE	1.05	1.02	0.97
LAUCI	0.97	1.08	1.11
LAUCT	0.98	1.09	1.12
LCMAX	1.03	1.16	1.12
THALF	0.95	0.98	1.03
TMAX	0.93	1.06	1.14

Table 42. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	382.42	390.39	362.25	0.98	1.06	1.08
AUCT	348.12	354.11	327.02	0.98	1.06	1.08
CMAX	23.63	22.91	21.13	1.03	1.12	1.08
LAUCI	363.78	371.59	338.13	0.98	1.08	1.10
LAUCT	328.97	334.77	300.54	0.98	1.09	1.11
LCMAX	23.28	22.38	20.15	1.04	1.16	1.11

C. Summary of Sequence Effects from PROC GLM

Significant sequence effects at the significance level of 0.1 were identified throughout the three studies only with LFLUC1 and LFLUC2 of desacetyl diltiazem under steady-state conditions.

VI. Product Information

1. Formulation

Test formulation for the 120 mg strength capsule is shown in Table 43. Granules are produced from the ingredients and these same granules are used to produce the 60 mg, 90 mg and 120 mg capsules. Inactive ingredients of the reference product consist of fumaric acid, povidone, starch, sucrose, talc, titanium dioxide, coloring agents and other ingredients.

Table 43. Test Formulation for 120 mg Strength

Ingredient	Content mg/tablet	w/w %
Diltiazem Hydrochloride, USP	120	46.8
Povidone, NF	(b)4 - Confidential Business	
Silicon Dioxide, NF		
Clear (b)4 -		
Sugar Spheres, NF		
Methacrylic Acid Copolymer, NF		
Diethyl Phthalate, NF		
Total	256.4	100

2. **Assay and content uniformity**

Table 44 summarizes assay and content uniformity data for the test and reference products.

Table 44. Assay and Content Uniformity

Product	Assay, %	Content Uniformity (%CV)
Mylan's Diltiazem Hydrochloride ER Capsules, 60 mg, lot #2B003L	101.8	101.4 (3.4)
Mylan's Diltiazem Hydrochloride ER Capsules, 90 mg, lot #2B004L	100.1	99.3 (2.0)
Mylan's Diltiazem Hydrochloride ER Capsules, 120 mg, lot #2B005L	99.9	99.7 (1.8)
Cardizem® SR Capsules, 120 mg, lot #P20228, Exp. 2/96	100.7	101.5 (3.2)

VII. Dissolution

Test and reference products met USP dissolution specifications as shown in Table 46. USP dissolution specifications are shown in Table 45:

Table 45. Dissolution Method

USP Method for Dissolution Testing USP Drug Release Test 4	
Medium and Volume	water; 900 mL
Apparatus and rpm	2 (paddle); 100 rpm
Time	4, 8, 12 and 24 hours
Tolerances	4 hrs 8 hrs 12 hrs 24 hrs (b)4 - Confident Business
Assay Method	(b)4 - Confidential

VIII. Waiver Request

The applicant requested a waiver for the 60 mg and 90 mg capsules. Based on the acceptable *in vivo* and *in vitro* dissolution data and proportionality of formulations, the waivers for the 60 mg and 90 mg capsules are granted.

IX. Comments

1. Study under Single Dose Fasting and Multiple Dose Steady-State Conditions (#9559): Twenty-eight healthy male volunteers were accepted for entry into the clinical phase of the study. Twenty-four subjects successfully completed both phases of the clinical portion of the study. Pharmacokinetic and statistical analyses were performed on the data for 23 subjects.

   Study under Nonfasting Conditions (#9572): Twenty-three healthy male volunteers were accepted for entry into the clinical phase of the study. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

2. Study under single dose fasting conditions: The 90% confidence intervals of LAUCT, LAUCI and LCMAX for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the

acceptable range of 80-125.

3. Study under steady-state conditions: The 90% confidence intervals of LAUCT, LCAVG, LCMAX, and LCMIN for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the acceptable range of 80-125.

4. Study under nonfasting conditions: The test/reference ratios of LAUCT, LAUCI and LCMAX under nonfasting conditions for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the acceptable range of 0.8-1.25.

5. Assay method validation data are acceptable.

6. Test products (60 mg, 90 mg and 120 mg strengths) met USP dissolution specifications.

7. Formulation: Three test formulations, 60 mg, 90 mg and 120 mg strengths, are proportional in active and inactive ingredients. The same granules were used to manufacture the 60 mg, 90 mg and 120 capsules.

8. There was no severe medical event which required a clinical action.

9. The batch size of the bio-batch (120 mg strength; lot #2B005L) was (b)4 - capsules.

10. Waivers are granted for the 60 mg and 90 mg capsules.

X. Deficiency

None.

XI. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting, steady-state and nonfasting conditions by Mylan on its Diltiazem Hydrochloride ER Capsules, 120 mg strength, lot #2B005L, comparing it to Hoechst Marion Roussel's Cardizem^{R} SR, 120 mg capsules, lot #P20228, have been found acceptable. The studies demonstrate that Mylan's Diltiazem Hydrochloride ER Capsules, 120 mg strength, is bioequivalent to the reference product, Hoechst Marion Roussel's Cardizem^{R} SR, 120 mg capsules.

2. The USP dissolution testing conducted by Mylan on its Diltiazem Hydrochloride ER Capsules, 120 mg strength, lot #2B005L, 90 mg strength, lot #2B004L, and 60 mg strength, lot #2B003L, is acceptable. The formulations for the 60 mg and 90 mg capsules are proportional to the 120 mg strength capsules of the test product which underwent an acceptable bioequivalence studies (submission date: 6/12/96). The waivers of *in vivo* bioequivalence study requirements for the 60 mg and 90 mg strength capsules of the test product are granted. The 60 mg and 90 mg strength capsules of the test product are ,therefore, deemed bioequivalent to the 60 mg and 90 mg strength capsules of Hoechst Marion Roussel's Cardizem^{R} SR.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (Paddle) at 100 rpm. The test product should meet the following specifications:

4 hrs	(b)4 -
8 hrs	onfidenti
12 hrs	
24 hrs	Business

4. From the bioequivalence point of view, the firm met the *in vivo* bioequivalence studies and *in vitro* dissolution testing requirements and the application is approvable.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 10/1/96

Ramakant M. Mhatre, Ph.D.
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Division of Bioequivalence

Concur: /S/ Date: 10/28/96

for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-910 (original, duplicate), Park, Drug File, Division File

File history: Draft (9/11/96); Final (9/27/96)

Table 46. *In Vitro* Dissolution Testing Data	
I. General Information	
Drug Product (Generic Name)	Diltiazem Hydrochloride ER Capsules
Strength	60, 90, and 120 mg Capsules
ANDA Number	74-910
Applicant	Mylan
Reference Drug Product	Cardizem[R] SR Capsules, 60, 90 and 120 mg
II. USP Method for Dissolution Testing USP Drug Release Test 4	
Medium and Volume	water; 900 mL
Apparatus and rpm	2 (paddle); 100 rpm
Time	4, 8, 12 and 24 hours
Tolerances	4 hrs 8 hrs 12 hrs 24 hrs (b)4 - Confidential Business
Assay Method	(b)4 -

III. Dissolution Data (%)

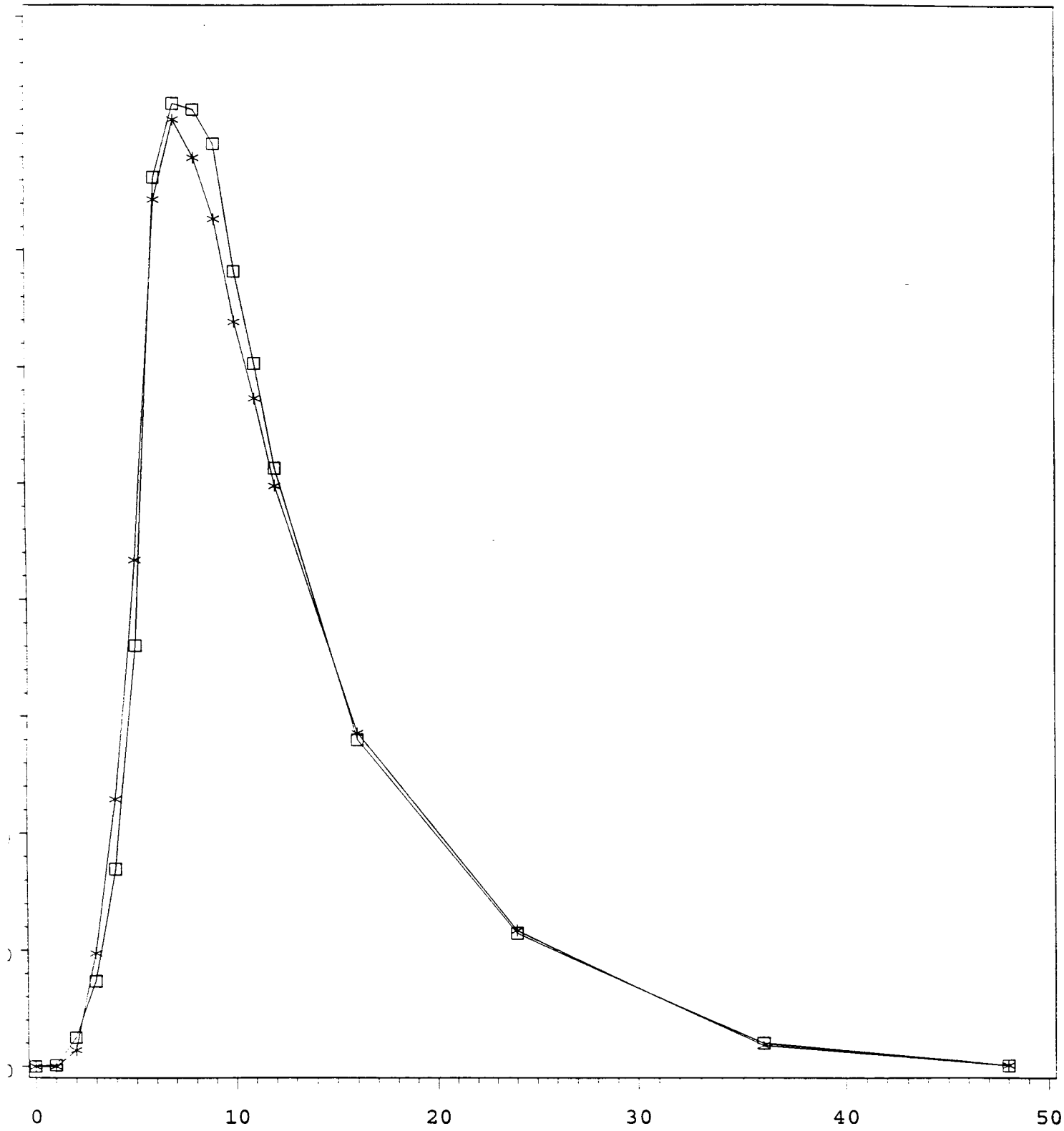
Time	Test Product Lot No: 2B003L Strength: 60 mg No of Units: 12			Reference Product Lot No: E01526 Strength: 60 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18	(b)4 - Confidential Business	7.4	33	(b)4 - Confidential Business	7.3
8	47		3.5	67		7.5
12	68		2.8	95		3.6
24	95		2.6	114		4.1

Time	Test Product Lot No: 2B004L Strength: 90 mg No of Units: 12			Reference Product Lot No: P10286 Strength: 90 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18	(b)4 - Confidential Business	12.3	34	(b)4 - Confidential Business	6.5
8	51		3.7	73		8.0
12	71		3.0	107		6.4
24	98		2.2	127		2.0

Time	Test Product Lot No: 2B005L Strength: 120 mg No of Units: 12			Reference Product Lot No: P20228 Strength: 120 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18	(b)4 - Confidential Business	6.2	24	(b)4 - Confidential Business	5.2
8	50		4.7	65		6.7
12	73		3.5	84		3.4
24	96		2.7	101		1.8

FIG P–1. PLASMA DILTIAZEM LEVELS

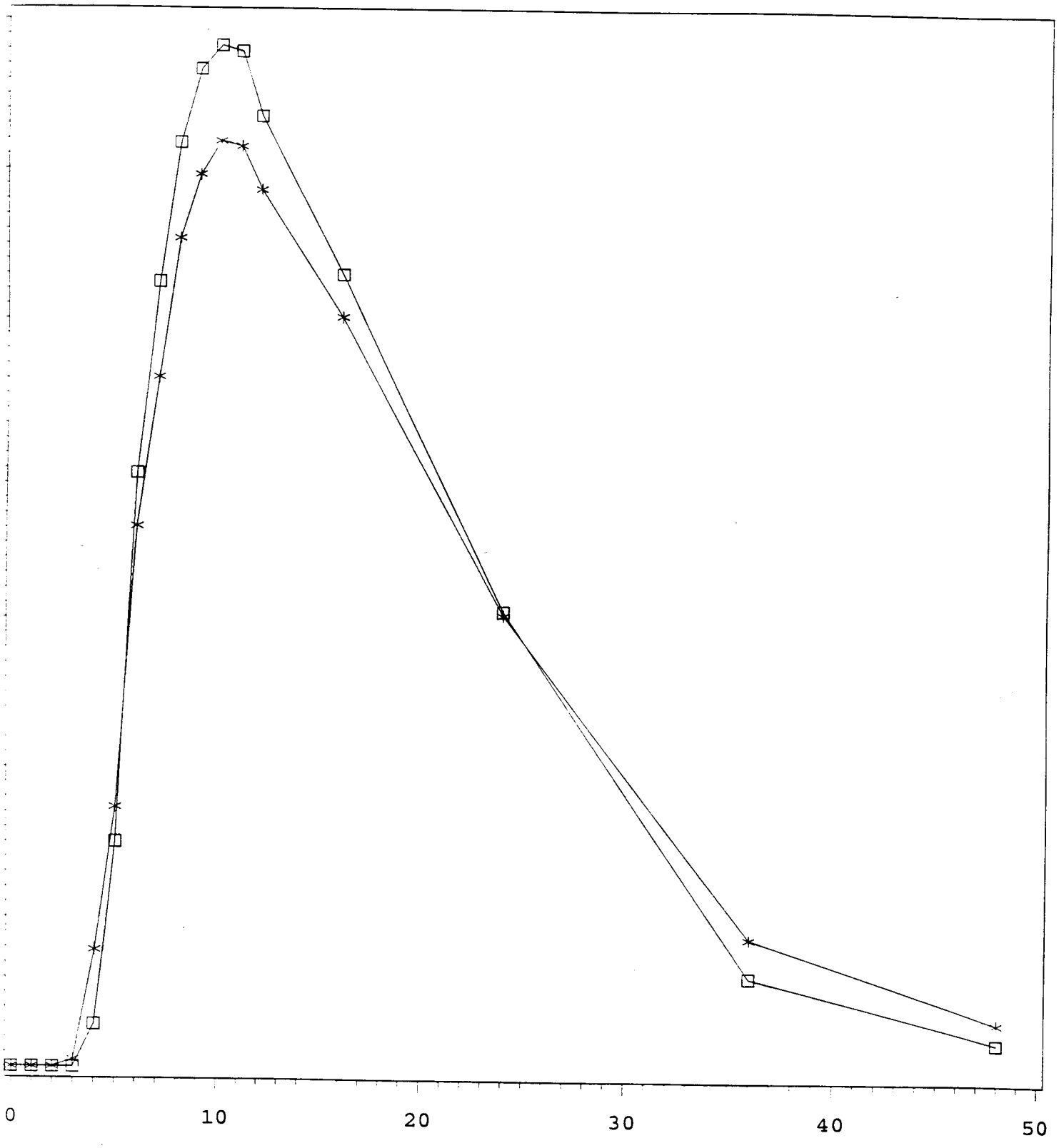
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

P-2. PLASMA DESACETYL DILTIAZEM LEVELS

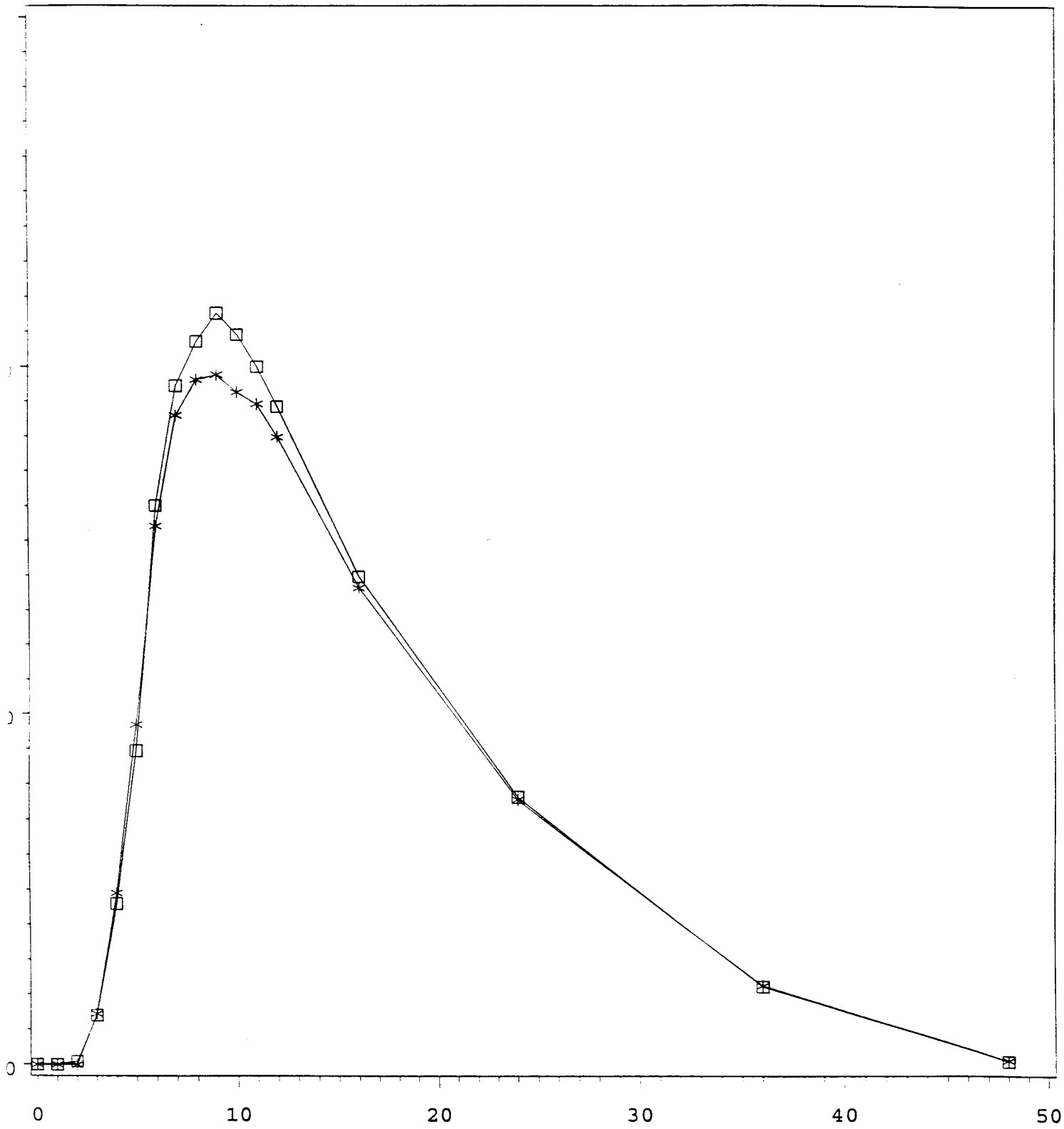
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

P-3. PLASMA DESMETHYL DILTIAZEM LEVELS

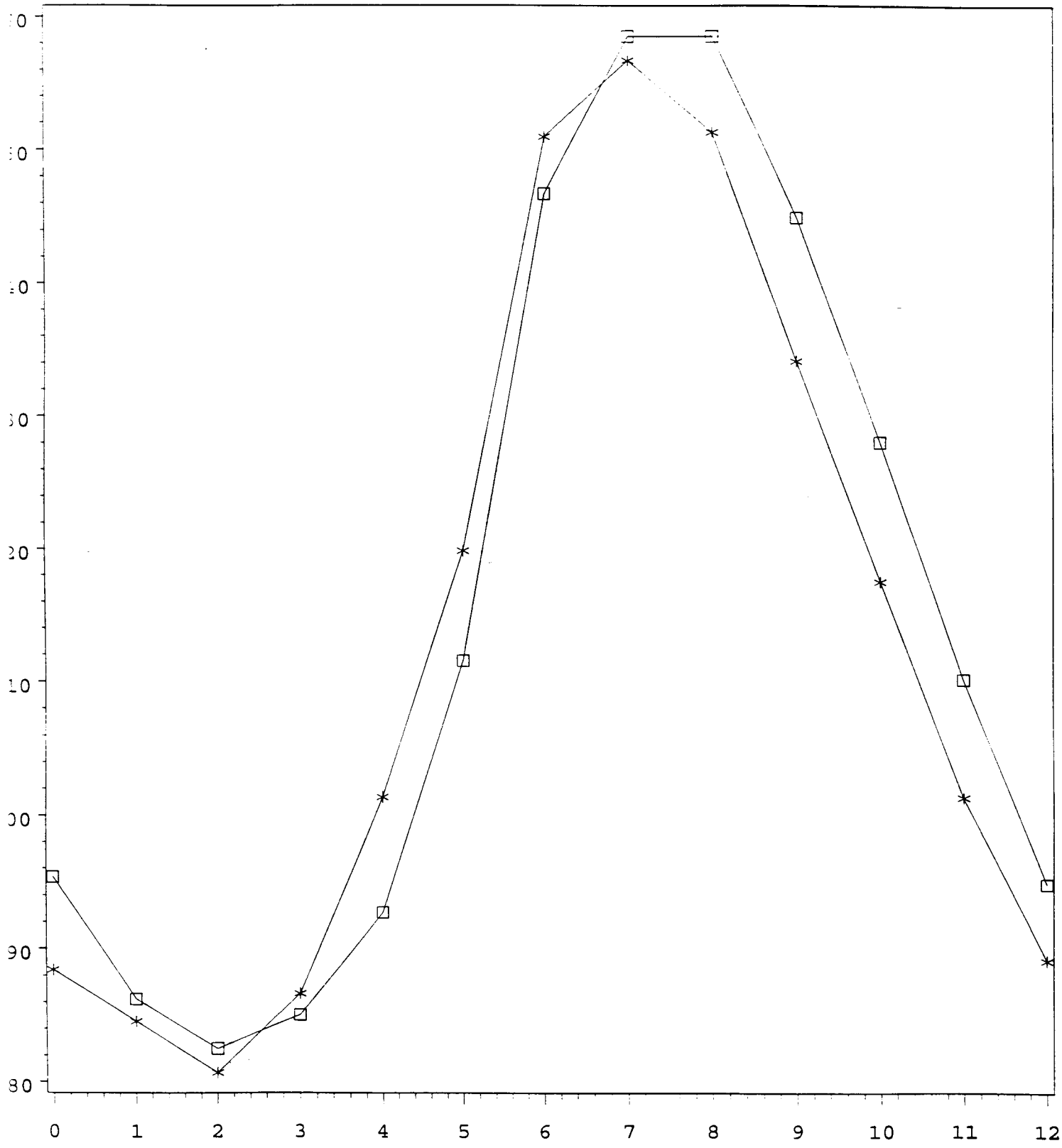
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

P-4. PLASMA DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

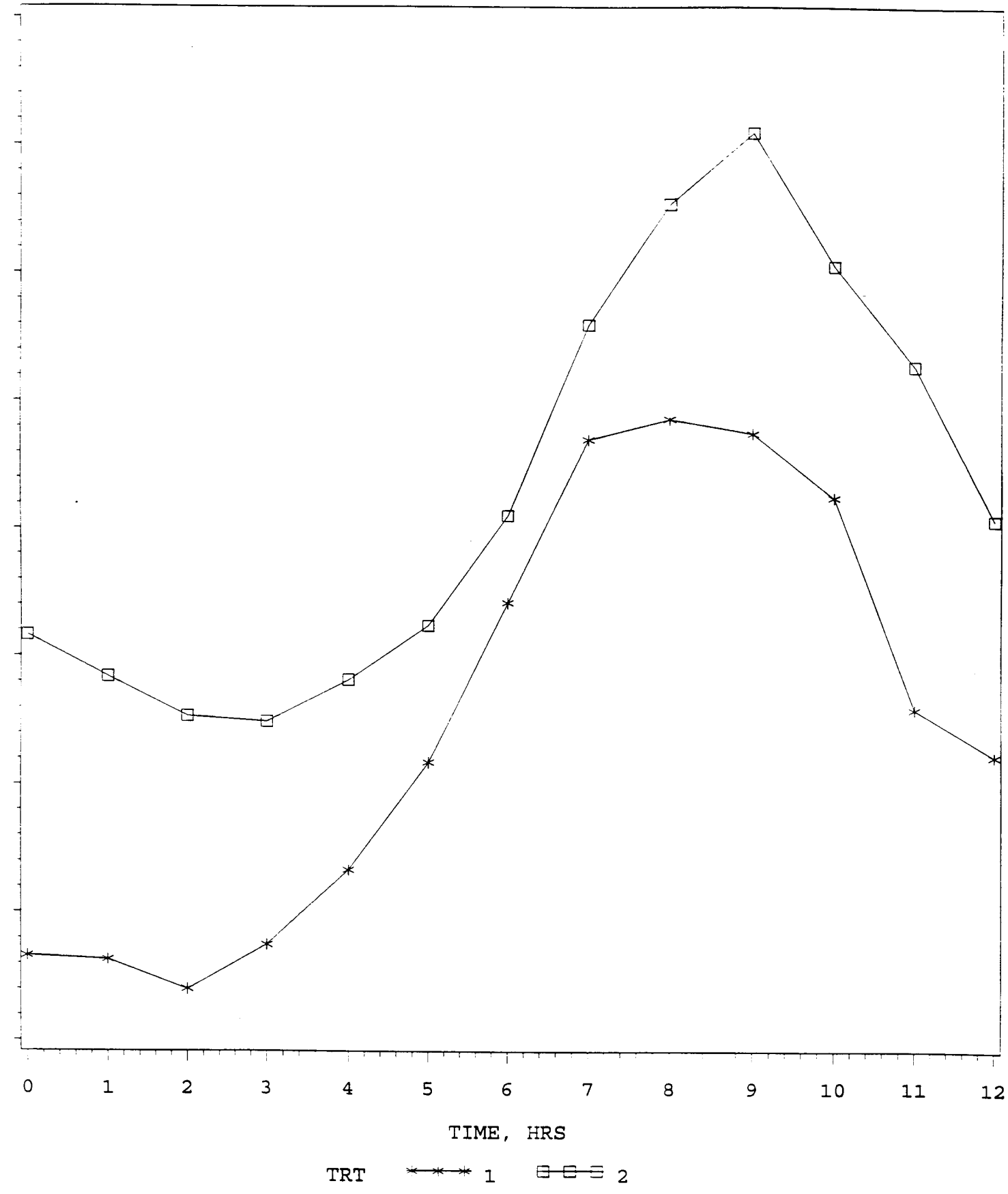
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

›–5. PLASMA DESACETYL DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

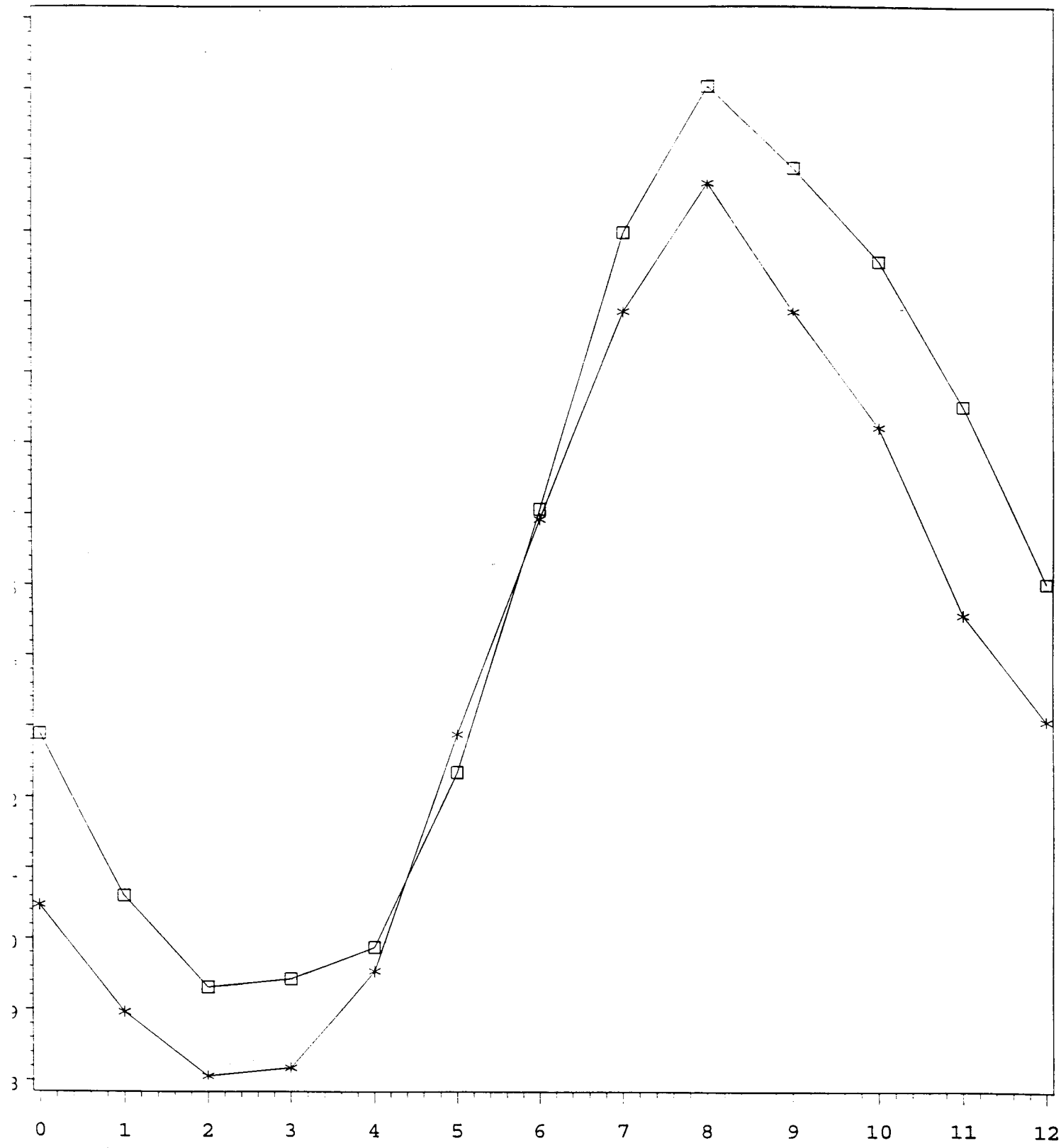
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

P-6. PLASMA DESMETHYL DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

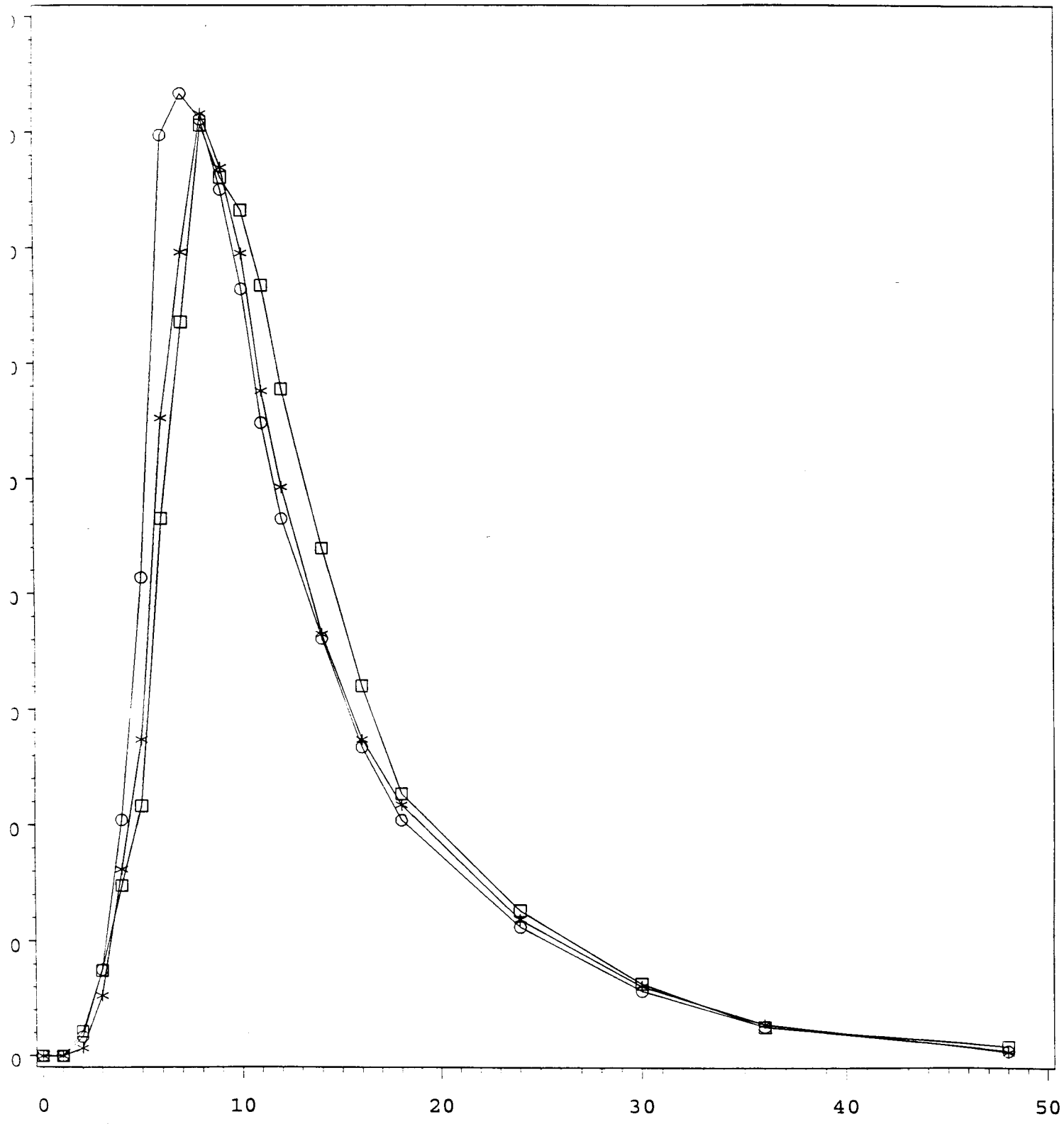
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

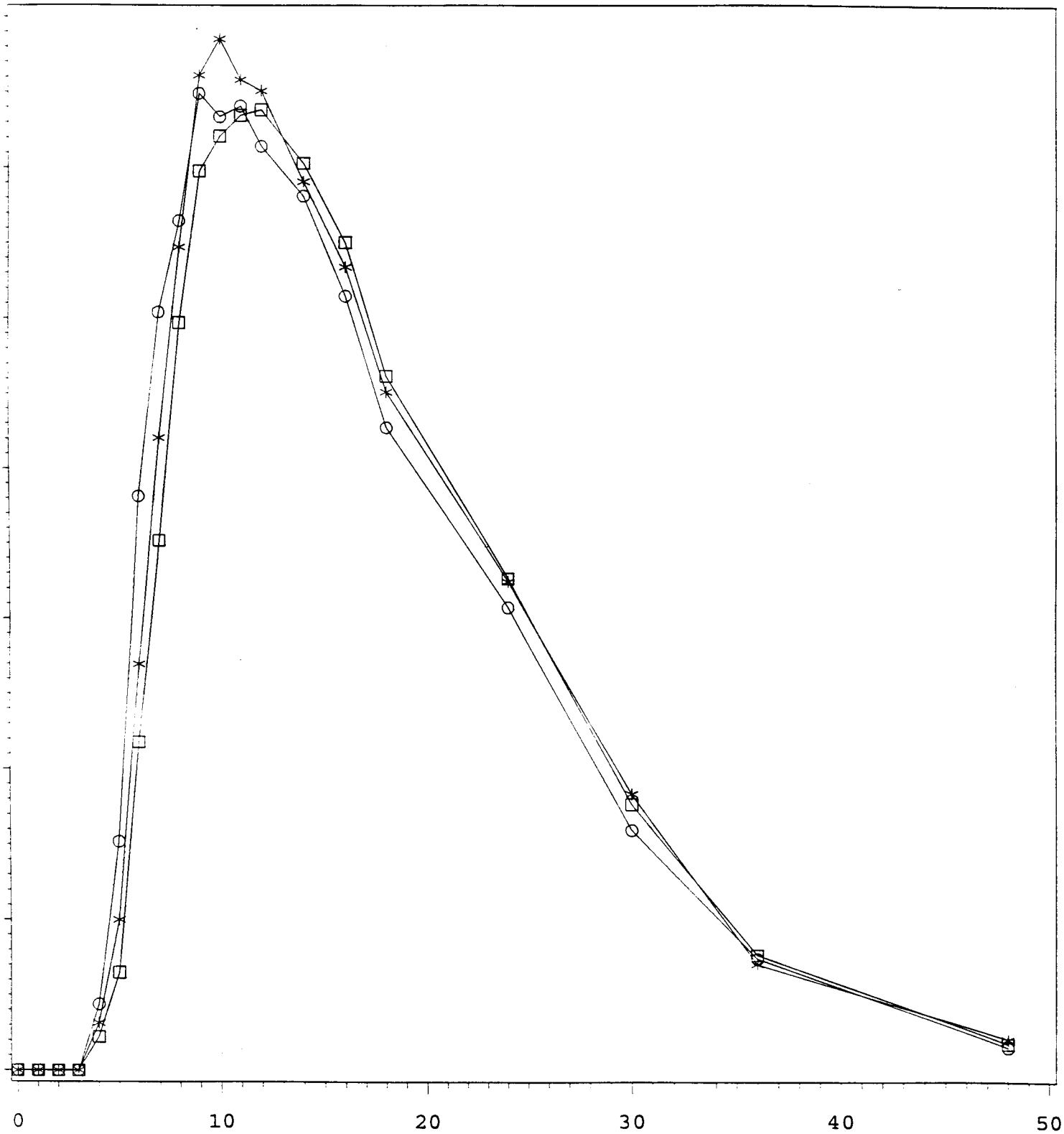
FIG P-7. PLASMA DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG



P-8. PLASMA DESACETYL DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST-FED(MYLAN) 2=REF-FED(HMR) 3=TEST-FAST(MYLAN)

G P−9. PLASMA DESMETHYL DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG